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AHA SCIENTIFIC STATEMENT

Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies

A Scientific Statement From the American Heart Association

ABSTRACT: Cardiorenal syndrome encompasses a spectrum of disorders involving both the heart and kidneys in which acute or chronic dysfunction in 1 organ may induce acute or chronic dysfunction in the other organ. It represents the confluence of heart-kidney interactions across several interfaces. These include the hemodynamic cross-talk between the failing heart and the response of the kidneys and vice versa, as well as alterations in neurohormonal markers and inflammatory molecular signatures characteristic of its clinical phenotypes. The mission of this scientific statement is to describe the epidemiology and pathogenesis of cardiorenal syndrome in the context of the continuously evolving nature of its clinicopathological description over the past decade. It also describes diagnostic and therapeutic strategies applicable to cardiorenal syndrome, summarizes cardiac-kidney interactions in special populations such as patients with diabetes mellitus and kidney transplant recipients, and emphasizes the role of palliative care in patients with cardiorenal syndrome. Finally, it outlines the need for a cardiorenal education track that will guide future cardiorenal trials and integrate the clinical and research needs of this important field in the future.

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The nuanced and highly interdependent relationship between the kidney and the heart was described as early as 1836 by Robert Bright, who outlined the significant cardiac structural changes seen in patients with advanced kidney disease.[1] Since then, numerous advances have been made in summarizing the cardiorenal link in terms of hemodynamic phenotypes, pathophysiology, therapeutic options, and clinical outcomes. The overlap of cardiovascular and kidney disease extends across several interfaces. These include the hemodynamic interactions of the heart and kidney in heart failure, the impact of atherosclerotic disease across both organ systems, neurohormonal activation, cytokines, the biochemical perturbations across the anemia–inflammation–bone mineral axis in chronic kidney disease (CKD), and structural changes in the heart unique to kidney disease progression. However, the term *cardiorenal syndrome* (CRS) encompasses a spectrum of disorders involving both the heart and kidneys in which acute or chronic dysfunction in 1 organ may induce acute or chronic dysfunction in the other organ. This scientific statement focuses primarily on the definition of, pathophysiology of, and diagnostic and therapeutic strategies in CRS. It also summarizes cardiorenal interactions in special populations such as patients with diabetes mellitus and kidney transplant (KT) recipients. Finally, it outlines the need for comprehensive cardiorenal trial end

Key Words: AHA Scientific Statements ■ acute kidney injury ■ biomarkers ■ cardio-renal syndrome ■ chronic kidney disease ■ dialysis ■ diuretics ■ heart failure ■ hospitalization ■ kidney transplantation ■ mortality ■ ultrafiltration

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points and the scope of a dedicated cardiorenal education track that will encapsulate the clinical and research needs of this important field for the future.

METHODOLOGY

The need for a comprehensive overview of the epidemiology of, pathophysiology of, diagnostic tools in, and therapeutic options for CRS was identified by the Council on the Kidney in Cardiovascular Disease of the American Heart Association (AHA). A writing group was commissioned to review the current literature and to develop an expert-based consensus summary on CRS. Members of the writing group were chosen for their expertise in heart failure, kidney disease, metabolic factors, and therapeutic strategies in the management of CRS. The writing group held a series of teleconferences and web-based communications from October 2017 tor2018. A manuscript outline was developed on the initial conference call, with individual section reviews being assigned to authors on the basis of their expertise. All authors had continuous access to the working document to provide input, and each section editor provided critical review and revisions.

The writing group used MEDLINE (1966–present) and the Cochrane Central Register of Controlled Trials as the primary sources for the literature search, which was limited to human subjects and the English language. Related article searches were conducted in MEDLINE to find additional relevant articles. In addition, writing group members recommended articles outside the scope of the formal searches.

Key relevant search words and Medical Subject Heading descriptors included *kidney disease*, *renal insufficiency*, *chronic renal/chronic kidney*, *acute kidney injury*, *end-stage renal* or *end-stage kidney disease, albuminuria*, *congestive/myocardial/heart failure*, *cardiomyopathy*, *cardiorenal*, *predialysism*, and *ultrafiltration*. Key search abbreviations included *CRS*, *CKD*, *CRF*, *CRD*, *AKI, RI*, *WRF*, *KT*, *CRT*, *ICD*, *CRT-D*, *ACEi/ARB*, *MRA*, *BB*, *ARNI*, *DM*, *T1DM*, *T2DM*, *SGLT-2 inhibitors*, *GLP-1 agonists*, *DPP-4 inhibitors*, *HF*, *HFrEF*, *HFpEF*, and *UF*. (A full list of abbreviations, including search terms used in the manuscript, is available as an Online Appendix.) Finally, findings from conference proceedings, medical textbooks, and relevant online data sources were also reviewed.

Certain topics within this statement may have been reviewed in other clinical practice guidelines and scientific statements published by other working groups, including AHA/American College of Cardiology task forces. When appropriate, these relevant guidelines have been referenced without the need to reiterate recommendations contained in those guidelines or statements. Suggestions/considerations agreed on by consensus within the writing group are included in specific areas when there is a desire to provide some guidance to the cardionephrology community.

CONFLICT OF INTEREST

The AHA has a strict conflict-of-interest policy for all writing groups Each writing group member declared all relevant current conflicts, and >50% of the writing group were free of relevant conflicts. The chair and vice chair did not have any relevant industry-related conflicts. The writing group members updated an electronic file of conflict-of-interest data from the beginning of the work until the article was published, and each member reported any new relevant conflicts at the beginning of each teleconference. See the Writing Group Disclosures table for details on individual conflict-of-interest reporting.

DEFINITION AND PHENOTYPES OF CRS

The first attempt at formally defining CRS came from the Working Group of the National Heart, Lung, and Blood Institute in 2004, which defined CRS as the result of interactions between the kidneys and other circulatory compartments that increase circulating volume, which exacerbates the symptoms of heart failure (HF) and disease progression.[2] The National Heart, Lung, and Blood Institute's definition also stated that at its extreme, cardiorenal dysregulation leads to CRS, in which therapy to relieve congestive symptoms of HF is limited by further decline in renal function. This cardiocentric definition remains the cornerstone of CRS as commonly observed in the setting of acute decompensated HF, now called acute HF (AHF). Recognizing a wider clinical spectrum that may represent cardiorenal dysregulation, the Acute Dialysis Quality Initiative outlined a consensus approach in 2008 that phenotyped CRS into 2 major groups, cardiorenal and renocardiac syndromes, based on the *primum movens* of the disease process.[3,4] This was further grouped into 5 subtypes based on disease acuity and sequential organ involvement, which are outlined in Table 1. The goals of this consensus definition of CRS were to facilitate reliable characterization of the clinical presentation of cardiorenal dysregulation for diagnostic and therapeutic purposes, to streamline inclusion criteria in epidemiological studies, to identify target treatment populations, and to develop novel diagnostic tools for the diagnosis and management of CRS.

The Acute Dialysis Quality Initiative classification of CRS overcame some of the initial ambiguity in defining CRS and helped clinicians deliver phenotype-based goal-directed therapies for CRS at the bedside. Although simplifying the clinical approach to CRS, it also recognized the inevitability of overlap between different phenotypes and the evolution of 1 subtype to the other during disease progression. However, in clinical practice, identifying the initial insult and subsequent events that result in decompensated acute or chronic CRS/renocardiac syndrome can be challenging. Several

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Table 1. Classification of CRS Based on the Consensus Conference of the Acute Dialysis Quality Initiative

Phenotype	Nomenclature	Description	Clinical Examples
Type 1 CRS	Acute CRS	HF resulting in AKI	ACS resulting in cardiogenic shock and AKI, AHF resulting in AKI
Type 2 CRS	Chronic CRS	Chronic HF resulting in CKD	Chronic HF
Type 3 CRS	Acute renocardiac syndrome	AKI resulting in AHF	HF in the setting of AKI from volume overload, inflammatory surge, and metabolic disturbances in uremia
Type 4 CRS	Chronic renocardiac syndrome	CKD resulting in chronic HF	LVH and HF from CKD-associated cardiomyopathy
Type 5 CRS	Secondary CRS	Systemic process resulting in HF and kidney failure	Amyloidosis, sepsis, cirrhosis

ACS indicates acute coronary syndrome; AHF, acute heart failure; AKI, acute kidney injury; CKD, chronic kidney disease; CRS, cardiorenal syndrome; HF, heart failure; and LVH, left ventricular hypertrophy.

complex interconnected pathways culminate in CRS, including diabetes mellitus, hypertension, HF, atherosclerosis, endothelial cell dysfunction, anemia and disorders of iron metabolism, and chronic inflammation, many of which do not have well-defined temporal progression patterns. To this end, an alternative classification of CRS based on the various clinical manifestations of CRS regardless of the initial organ of injury was proposed by Hatamizadeh et al[5] that encompasses manifestations of hemodynamic compromise, uremic or vascular manifestations, neurohumoral disturbances, anemia/iron and bone mineral metabolism perturbations, and the malnutrition inflammation complex.

Determining the significance of fluctuations in kidney function that meet the criteria for acute kidney injury (AKI) in the context of CRS represents a core challenge in standardizing its definition and phenotypes, particularly in the setting of AHF, in which decongestive therapies may complicate the assessment of biomarkers of renal function (especially for serum creatinine and urine output). Historically, the description of an acute decline in kidney function in the CRS literature has included the use of inconsistent terms such as kidney impairment and renal insufficiency, thus limiting accurate quantification of kidney injury and its clinical significance in a consistent fashion. Initial efforts toward standardizing the definition of AKI through the use of the RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease [ESKD]) criteria came from the Acute Dialysis Quality Initiative in 2002[6] and were subsequently modified by the Acute Kidney Injury Network.[7] The 2012 Kidney Disease: Improving Global Outcomes guideline on the evaluation and management of AKI harmonized these 2 sets of criteria to allow early AKI detection, to permit epidemiological comparisons, and to standardize entry criteria and end points in clinical trials.[8]

The standardized criteria for the diagnosis of AKI greatly improved the sensitivity of detection of AKI with emphasis on small fluctuations in serum creatinine and urine output; however, they may not represent true renal tubular injury when observed in the context of diuresis in the setting of AHF. Ahmad et al[9] demonstrated that tubular injury quantified by validated urine biomarkers was not associated with worsening renal function estimated with cystatin C (CysC) with aggressive diuresis in patients with AHF. These findings suggest that small to moderate fluctuations in measurements of renal function with clinically available biomarkers (such as serum creatinine) in the context of aggressive diuresis in AHF may be dissimilar from other causes of AKI such as sepsis or drug-induced nephrotoxicity. Thus, underpinning the difference between true AKI with evidence of tubular injury and pseudo-AKI or worsened renal function from functional changes in estimated glomerular filtration rate (eGFR) is critical in preventing suboptimal delivery of appropriate goal-directed therapies such as decongestion and renin-angiotensin-aldosterone system (RAAS) inhibition in CRS.[10] The cornerstone in making this distinction between AKI and worsened renal function (without injury) in the setting of AHF, azotemia, and declining urine output rests on a combination of clinical assessment of perfusion status, relevant hemodynamic parameters (invasive and noninvasive), detection of bedside markers of intrinsic renal injury evident on urine microscopy, and a thorough investigation of alternative explanations for worsening renal function. In the absence of evidence for intrinsic causes of kidney injury, small fluctuations in serum creatinine in the context of delivering appropriate goal-directed therapies in AHF may not have the same negative prognostic impact of AKI as seen with alternative causes[9] and may represent the effect of relative plasma underfilling or the therapeutic intended target effects of medical therapies for AHF, which are outlined in subsequent sections. To this end, the incorporation of novel biomarkers of cardiac and kidney injury to delineate the presence (or absence) of organ damage and to guide therapeutic strategies in CRS represents a new dimension in improving the accuracy of the definition of CRS and its treatment targets for the future.

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PATHOPHYSIOLOGICAL MECHANISMS IN CRS

The conventional explanation for the development of CRS in the setting of a cardiocentric *primum movens* focuses on the inability of the failing heart to generate forward flow, thus resulting in prerenal hypoperfusion. Inadequate renal afferent flow activates the RAAS axis, the sympathetic nervous system, and arginine vasopressin secretion, leading to fluid retention, increased preload, and worsening pump failure.[11] However, the presence of a low-flow state only partly explains the pathophysiology of CRS. The ADHERE registry (Acute Decompensated Heart Failure National Registry) noted that the incidence of rising serum creatinine was similar among patients with AHF and reduced versus preserved systolic function.[12] In addition, many patients hospitalized with evidence of acute CRS have preserved or even elevated blood pressure and normal left ventricular (LV) ejection fraction (EF).[13] The kidneys are not first in line for delivery of oxygenated blood, yet they receive a disproportionately large fraction (25%) of cardiac output (CO) because they are a low-resistance circuit. The difference between arterial driving pressure and venous outflow pressures must remain sufficiently large for adequate renal blood flow and glomerular filtration. In this context, the concept of elevated central venous pressures (CVPs) resulting in renal venous hypertension, increased renal resistance, and ultimately impaired intrarenal blood flow has been shown in early experimental models[14] and in more contemporary experiences in patients with AHF using invasive hemodynamic monitoring.[15,16] Merrill[17] elegantly demonstrated large reductions in renal blood flow in subjects with decompensated HF with relative preservation of glomerular filtration rate (GFR). This was explained by a concomitant increase in filtration fraction derived from elevated intraglomerular pressures from efferent arteriolar constriction in the setting of elevated renin levels. However, in severe decompensated HF with markedly elevated renal venous pressures and decreased renal blood flow, the compensatory increase in filtration fraction is lost and results in declining GFR.[18] In this setting, the decrease in intraglomerular pressures and reduced GFR are driven by preglomerular vasoconstriction from extreme levels of RAAS and neurohumoral activation. In addition, the enhanced activation of the neurohumoral axis results in increased proximal tubular sodium and water reabsorption to maintain effective plasma volumes, eventually resulting in oliguria and worsening congestion.[19] These renal hemodynamic regulatory mechanisms are also the rationale behind the elevations in serum creatinine from decreased glomerular hydraulic pressures seen with the administration of RAAS inhibitors, with little changes in renal blood flow per se, and translate into true worsening of renal function only when reductions in mean arterial pressure exceed renal autoregulatory capacity.[18,20] This is the basis for the elevations in serum creatinine seen with RAAS inhibition in trials such as CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study), which is discussed further in the RAAS Inhibition in Chronic CRS section on pharmacotherapies.[21] Finally, the low-resistance nature of the renal vasculature and parenchyma and the very low oxygen tension in the outer medulla also explain the unique sensitivity of the kidneys to hypotension-induced injury. Thus, both hemodynamic instability and antecedent hypotension should be considered in the consultative evaluation of a patient with developing CRS.

In a post hoc analysis of the ESCAPE trial (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness), right atrial (RA) pressure was the only hemodynamic parameter associated with baseline renal dysfunction.[22] This observation was also confirmed in a broad spectrum of cardiovascular patients undergoing right-sided heart catheterization, in whom increased CVP was associated with reduced GFR and all-cause mortality.[23] Along the same lines, elevated intra-abdominal pressures (IAPs) in the setting of AHF may contribute to renal dysfunction by causing renal compression and reduced perfusion.[24] Hemodynamic metrics reflective of right ventricular (RV) function such as the RV stroke work index may have prognostic impact on kidney function in HF (including in patients with HF with preserved ejection fraction [HFpEF]), thus underscoring the influence of RV function on renal hemodynamics.[25] However, data on the neurohumoral perturbations and sodium and water retention in isolated RV failure models in humans are scarce. Early experimental models inducing RV failure by graded valvular damage showed a decrease in renal blood flow, preserved GFR, and intense salt and water retention.[26] Other investigators have shown that despite the presence of pulmonary baroreceptors, when CO is kept constant, pulmonary arterial (PA) distension did not have a direct effect on renal hemodynamics.[27] The renal hemodynamic changes and the retention of sodium and water observed in patients with PA hypertension therefore may be mediated by systemic rather than PA baroreceptors, as has been shown in other edematous states.[28] Thus, in the clinical context of CRS, the relative effects of declining RV function and elevated RV afterload on renal hemodynamics are less clear. The cardiorenal neural reflexes initiating from the PA circulation or the RV have not been well delineated, and the elevated levels of natriuretic peptides seen with PA hypertension/RV dysfunction do not account for the sodium avid state seen in RV failure, albeit their negative prognostic significance.[29,30] Other mechanisms of the direct effect of RV dysfunction on renal hemodynamics include interventricular asynchrony and pericardium-mediated RV-LV interactions. This is a consequence of prolonged

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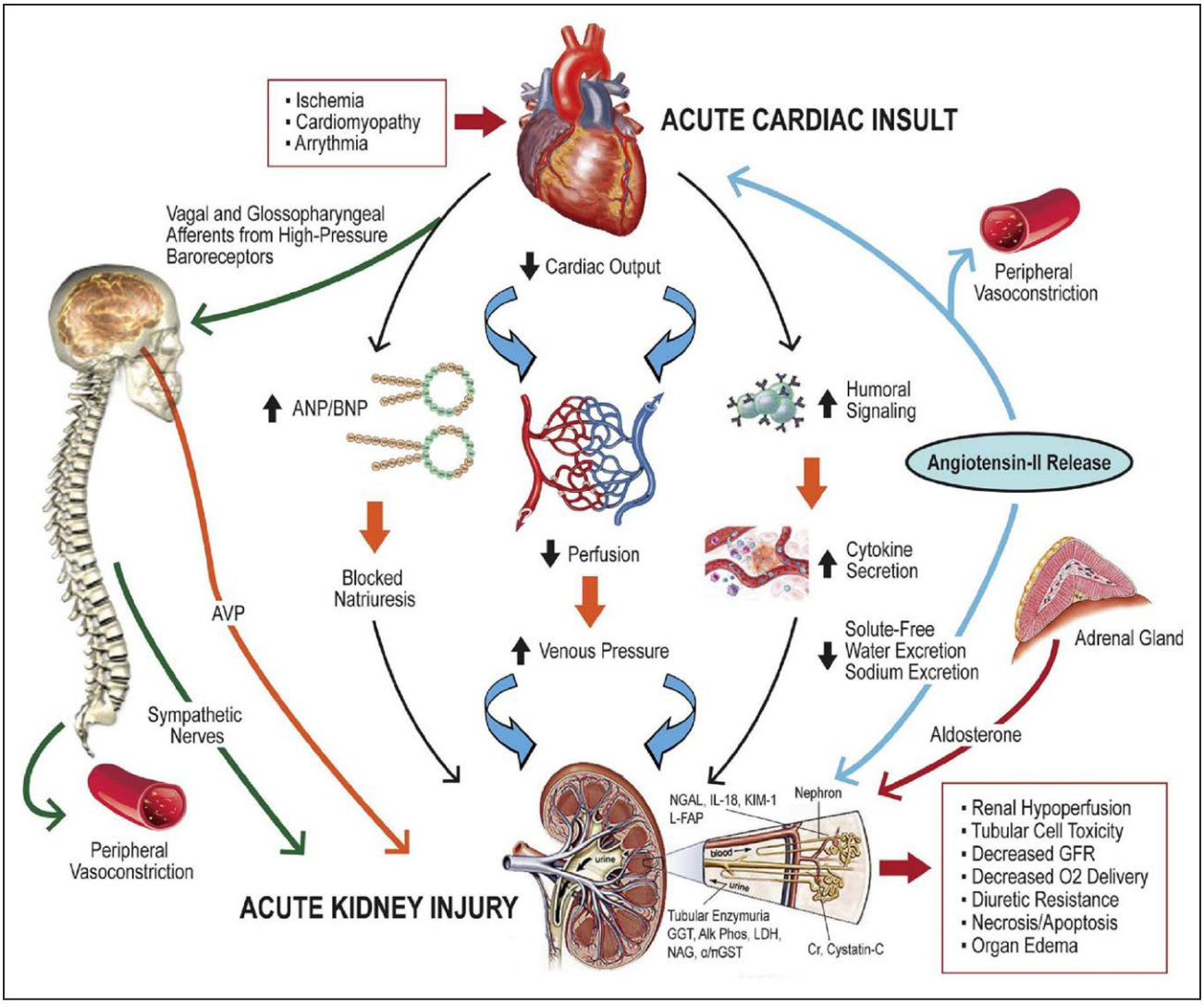

Figure 1. Pathophysiology of neurohumoral and inflammatory pathways involved in cardiorenal syndrome.
α/π GST indicates α/π glutathione S-transferase; Alk Phos, alkaline phosphatase; ANP, atrial natriuretic peptide; AVP, arginine vasopressin; BNP, B-type natriuretic peptide; Cr, creatinine; GFR, glomerular filtration rate; GGT, γ-glutamyl transferase; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; LDH, lactate dehydrogenase; L-FAP, L-type fatty acid protein; NAG, N-acetyl-β-D-glucosaminidase; and NGAL, neutrophil gelatinase-associated lipocalin. Reprinted from Ismail et al[39] with permission from Elsevier. Copyright © 2012, Elsevier.

contraction of the RV free wall seen with RV pressure overload exceeding LV pressures in early diastole, resulting in paradoxical septal movement, which causes reduced LV end-diastolic filling.[31,32] Finally, although RV function is a central determinant of CRS hemodynamics, surgical models such as the Fontan procedure demonstrate the ability to maintain CO and functional capacity by bypassing the RV in the presence of normal LV function and the absence of pulmonary vascular disease.[33,34]

Several nonhemodynamic pathways that exacerbate cardiac or kidney injury are operative in CRS, central to which are activation of the sympathetic nervous system, chronic inflammation, imbalance in the proportion of reactive oxygen species/nitric oxide production, and persistent RAAS activation.[35] Circulating levels of TNF-α (tumor necrosis factor-α), IL-1 (interleukin-1), and IL-6 (interleukin-6), which are elevated in experimental models of AKI, have direct cardiodepressant effects such as a reduction in LVEF. Uremic cardiomyopathy (type 4 CRS) is characterized by significant burden of LV hypertrophy on which FGF-23 (fibroblast growth factor-23) has recently been shown to have an independent causal effect.[36] Because the hypertrophy of the LV is associated with a reduction in capillary density, particularly in the central endocardium, it is conceivable that microvascular ischemia plays a role in the progression of uremic cardiopathy. Endothelial stretch from peripheral venous congestion causes conversion of vascular endothelium from a quiescent to a proinflammatory phenotype, highlighting the importance of decongestion in CRS beyond its hemodynamic effects.[37] Finally, data are emerging on the cross-talk between cardiac and kidney dendritic cells, which play a central role in innate and

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adaptive immune responses in the context of CRS.[38] The key pathophysiological pathways involved in CRS are outlined in Figure 1.[39]

DIAGNOSTIC STRATEGIES IN CRS

HF is a complex mechanical and neurohumoral syndrome resulting in stasis of blood in the lungs and periphery, causing the cardinal features of effort intolerance and edema. Diagnosis of HF requires the presence of signs and symptoms, along with evidence of a structural or functional cardiac abnormality,[40] and in CRS, this requirement extends to the heart and kidneys. Several diagnostic tools help establish the structural and functional derangements characteristic of CRS, including biomarkers, noninvasive imaging modalities, invasive hemodynamic monitoring, and adjuvant volume measurement techniques, which are summarized in the following sections.

Biomarkers

Biomarkers of cardiac and kidney injury may provide valuable information when applied to the clinical context of CRS and can serve to indicate early cardiac or renal injury, the repair process, and long-term sequelae.[41] They represent an opportunity to prognosticate CRS, to discriminate between CRS phenotypes, and to serve as markers for targeted therapeutic interventions. Although biomarkers of myocardial injury (troponin) and wall tension (BNP [B-type natriuretic peptide]/NT-proBNP [N-terminal pro-BNP]) are routinely used in clinical practice, biomarkers of AKI are emerging as an additional dimension in diagnostic algorithms. The definitions of AKI used today are linked to changes in creatinine or urine output, resulting in a significant time lag of 24 to 48 hours to institute corrective measures. Table 2 summarizes key biomarkers of CRS based on site of origin and diagnostic and prognostic value in AKI, HF, and, when applicable, CRS.

Renal Biomarkers in CRS

Markers of Glomerular Filtration and Integrity

CysC and albuminuria represent biomarkers of glomerular filtration and integrity in CRS. CysC is a 13-kDa cysteine protease, ubiquitous in all nucleated cells, that is produced at a constant rate, freely filtered, completely reabsorbed, and not secreted in renal tubules. In a subset of patients with chronic HF in the Cardiovascular Health Study, the highest quartile of serum CysC (>1.55 mg/L) was associated with twice the risk of cardiovascular mortality adjusted for baseline characteristics.[42] In patients presenting with AHF, serum CysC was a strong indicator of rehospitalization and short- and long-term mortality[43,44] and had additive prognostic value when combined with other CRS biomarkers such as NT-proBNP and cardiac troponin T.[45] Similarly, albuminuria had a strong prognostic value for all-cause mortality, cardiovascular death, and readmission in patients with HF in substudies of 3 major HF trials: CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity), GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca–Heart Failure), and Val-HeFT (Valsartan in Heart Failure).[46–49] It is important to note that biomarkers of glomerular integrity such as serum creatinine and CysC have differing sources of bias when estimating GFR, particularly in advanced CRS.[50,51] To this end, measurement of tubular secretory clearance may provide different metabolic profiles of retained solutes eliminated by tubular secretion and filtration (eg, indoxyl sulfate and p-cresyl sulfate) and thus refine the approach to quantification of kidney function and drug dosing and improve prediction of cardiovascular disease and kidney outcomes.[52]

Markers of Renal Tubular Injury

Urine microscopy is a readily available clinical biomarker that has diagnostic value in distinguishing an intrinsic cause of AKI from functional changes in serum creatinine in the setting of AHF. In addition, a urine sediment severity score based on the number of renal tubular epithelial cells and granular casts was shown to have prognostic value in the prediction of worsening AKI during hospitalization.[53] Several novel urinary biomarkers have shown promise in identifying tubular injury in AKI; some assays are available for in vitro use and are briefly described below.

NGAL (neutrophil gelatinase-associated lipocalin), a 25-kDa protein found in neutrophil granules that is secreted by renal tubular epithelium, myocardial cells, and other specific organ sites, has been extensively studied in CRS and has diagnostic and prognostic value in AHF and chronic HF. NGAL is the most upregulated protein produced by the kidneys in the setting of AKI. A meta-analysis of 10 studies involving ≈2000 patients with predominantly CRS identified early serum and urine NGAL measurements as predictors of dialysis and death with a pooled area under the curve of 0.78 and 0.75, respectively.[54] Serial measurements of NGAL in AHF increase its predictive value for AKI, with the change in NGAL from baseline to peak producing an area under the curve of 0.91 compared with 0.69 for NGAL at admission only.[55] NGAL assays are available for clinical use outside but not within the United States.

The combination of TIMP-2 (tissue inhibitor of metalloproteinase-2) and IGFBP7 (insulin-like growth factor–binding protein 7), both tubular biomarkers involved in G1 cell cycle arrest during the early phase of cell injury, is available for clinical use in the United States. Kashani et al[56] compared the performance of TIMP-2 and IGFBP7 in combination with other biomarkers of AKI in the SAPPHIRE validation cohort (Systolic and Pulse Pressure Hemodynamic Improvement by Restoring Elasticity) in

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Table 2. Biomarkers of Renal and Cardiac Injury Based on Site of Origin and Diagnostic and Prognostic Roles in AKI, HF, and CRS

Biomarkers	Characteristics/Site of Origin	Diagnostic Value	Prognostic Value
Cardiac biomarkers			
cTn	Marker of myocardial injury	ACS	ACS, HF, CKD
BNP	Marker of myocardial stretch	HF, ACS, CRS	HF, CRS
sST2	Member of IL-1 family of receptors	…	HF, CRS
Galectin-3	β-Galactoside binding lectin (intracellular and extracellular)	…	HF, CRS
Kidney biomarkers			
Biomarkers of glomerular integrity			
Serum creatinine	Skeletal muscle	AKI, CRS	HF, CRS
CysC	All nucleated cells	CRS	CRS
Albuminuria	Marker of glomerular integrity/PCT disruption	CRS	CRS
Biomarkers of tubular injury			
TIMP*IGFBP7	Involved in G1 cell cycle arrest; may stimulate renal epithelium in an autocrine and paracrine fashion and sensitize for upcoming insults	AKI	AKI recovery
Serum NGAL	25-kDa protein found in neutrophil granules; secreted by myocardium, renal tubules, activated immune cells, hepatocytes, lung, and colon	AKI	CRS
Urine NGAL	Loop of Henle, collecting ducts	AKI, CRS	CRS
NAG	PCT	CRS, AKI	CRS
KIM-1	Type 1 cell membrane glycoprotein expressed in regenerating PCT epithelium	AKI	CRS
IL-18	Cytokine mediating inflammation and AKI through the nuclear factor-κB pathway	AKI	CRS
L-FABP	Renal PCT	AKI	…
H-FABP	Cardiomyocytes, distal tubule	HF, CRS	…
Urine angiotensinogen	…	AKI, CRS	CRS
α-1 Microglobulin	Synthesized in liver; freely filtered through glomerular capillaries and reabsorbed by PCT	AKI	AKI recovery

ACS indicates acute coronary syndrome; AKI, acute kidney injury; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; CRS, cardiorenal syndrome; cTn, cardiac troponin; CysC, cystatin C; ellipses (…), data not available or reported.; HF, heart failure; H-FABP, heart-type fatty acid–binding protein; IGFBP7, insulin-like growth factor protein 7; IL, interleukin; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid–binding protein; NAG, N-acetyl-κ-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; PCT, proximal convoluted tubule; sST2, soluble suppressor of tumorigenicity; and TIMP, tissue inhibitor of metalloproteinase.

728 critically ill patients without evidence of AKI at enrollment. In this study, the combination of urine TIMP-2 and IGFBP7 was superior to previously described markers of AKI ($P<0.002$). Although the performance of TIMP-2 and IGFBP7 has been validated in several settings of AKI, the relationship between cell cycle arrest markers and CRS has not yet been described, and there are no reported studies of this biomarker combination measured serially in AHF. The promising markers of tubular injury in AKI and their specific role in CRS (if available) are summarized in Table 2.

Urinary biomarkers that correlate with measures of congestion such as BNP or NT-proBNP may play a role in phenotyping CRS in AHF and guide decongestive therapies.[57] Perhaps the most critical role that novel AKI markers can have is in their negative predictive value in distinguishing functional serum creatinine fluctuations from true AKI. This distinction at the bedside may influence or even guide the delivery of goal-directed therapy in CRS in the future; however, tubular biomarkers are influenced by the degree of baseline functioning renal tissue and thus may be inaccurate at low filtration rates, representing an important limitation of these markers. Finally, biomarkers that represent the transition to chronicity on the AKI-CKD continuum may help phenotype the shift from acute to chronic CRS and assist with appropriate clinical therapies and prognostication.

Cardiac Biomarkers in CRS

The "2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure" reiterated the existing Class 1A recommendation for the use of BNP and its inactive cleavage proBNP in the diagnosis/exclusion of HF, as well as establishing prognosis and quantifying severity in AHF and chronic HF.[58] Patients with CKD have higher

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baseline BNP levels compared with matched patients with normal renal function because of impaired renal clearance (more notably with NT-proBNP), as well as chronic pressure/volume overload and CKD-associated cardiomyopathy.[59,60] BNP levels are also significantly elevated in patients with evidence of CRS compared with patients with AHF without renal impairment.[61] Future studies are necessary to determine the interpretation of fluctuations in natriuretic peptide levels in the context of administration of angiotensin receptor blocker (ARB)/neprilysin inhibitor therapy, especially in patients with CRS.[62]

ST2 (suppressor of tumorigenicity 2) is a decoy protein produced by the endothelial cells lining the LV and aortic outflow tract in response to biomechanical strain. ST2 binds to the IL-33 (interleukin-33) receptor on cardiomyocytes and satellite cells in the heart, and instead of receiving favorable signal transduction, the ST2 effect results in myocyte dysfunction and tissue fibrosis. ST2 measurements offer incremental value to natriuretic peptides levels in predicting HF-related deaths and hospitalizations and notably are not affected by renal function.[58]

Galectin-3 is a member of the β-galactoside–binding lectin family that is synthesized by cardiac macrophages and known to interact with specific extracellular matrix proteins, including laminin, synexin, and integrins. In a recent study of 232 patients with New York Heart Association (NYHA) class III or IV HF, Lok et al[63] used NT-proBNP and eGFR to adjust for severity of heart disease and degree of renal dysfunction and demonstrated that serum galectin-3 levels were independent predictors of cardiovascular mortality.[64] In a secondary analysis of the CORONA trial (Controlled Rosuvastatin Multinational Trial in Heart Failure) and COACH trial (Coordinating Study Evaluating Outcomes of Advising and Counseling Failure), patients whose galectin-3 levels increased by >15% over 3 to 6 months had a significantly increased adjusted risk for all-cause mortality and hospitalization for HF (HHF).[65] Tang et al[66] reported in a single-center study of subjects with chronic HF that higher galectin-3 levels were associated with worse renal function and poorer survival and that galectin-3 remained an independent predictor of all-cause mortality in a multivariate analysis of several factors, including eGFR.

High-sensitivity cardiac troponins I and T are established diagnostic and prognostic markers in acute myocardial infarction (MI). In addition to their diagnostic value, cardiac troponins have prognostic implications when elevated in acute decompensated HF even in the absence of myocardial ischemia or underlying coronary artery disease, and elevated levels are associated with a higher risk of death.[58] The prevalence of elevated cardiac troponins increases with declining GFR, and a sustained elevation is associated with a higher mortality risk.[67]

Imaging Modalities

Up to 40% of patients hospitalized for AHF present with a type 1 CRS phenotype.[68] Reduction in renal perfusion pressure from elevated CVP plays a critical role, along with reduced CO in the pathogenesis of AKI in CRS.[15] Noninvasive imaging modalities play an important role in establishing markers of venous congestion and impaired forward flow in CRS and are readily accessible clinical tools at the bedside. Echocardiography may help in diagnosing the congestive state by hemodynamic parameters, including CVP, systolic PA pressure, pulmonary capillary wedge pressure/left atrial pressure, and CO.[69] Besides CVP, other useful echocardiographic measurements include lateral and septal wall longitudinal motion (E′) in relation to the mitral inflow velocity (E). The E/E′ ratio directly correlates with pulmonary capillary wedge pressure, with an E/E′ >15 correlating to a pulmonary capillary wedge pressure of ≥18 mm Hg.[70,71] In addition, echocardiography carries prognostic value specific to phenotypes in CRS. In a retrospective cohort study in a large healthcare system, acute CRS (types 1 and 3) was associated with the highest risk of death compared with CKD without CRS (hazard ratio [HR], 3.13 [95% CI, 2.72–3.61]).[72] Patients with CRS type 4 had better survival than patients with acute CRS (HR, 0.48 [95% CI, 0.37–0.61]). Sixteen percent of patients with type 2 CRS and 20% of patients with type 4 CRS developed acute CRS, whereas 14% of patients with acute CRS progressed to CKD or chronic HF. Decreasing LVEF, increasing PA pressure, and higher RV diameter were independently associated with higher incidence of CRS.

Renal ultrasonography and intrarenal venous flow patterns are emerging tools in identifying renal venous congestion and its clinical significance in CRS. Iida et al[73] examined intrarenal venous flow patterns measured by intrarenal Doppler ultrasound that were associated with RA pressures and correlated strongly with clinical outcomes. In their study cohort of 217 patients hospitalized with AHF, 54% of subjects exhibited a continuous intrarenal venous flow pattern that invariably had low RA pressures (estimated <10 mm Hg) and favorable prognosis (>95% survival at 1 year). In contrast, about one-quarter of patients with discontinuous intrarenal venous flow, with either increased RA pressures (26%) or monophasic patterns (23%), had the poorest prognosis (<40% survival at 1 year).[73] In subjects with HF, intravascular expansion results in significant blunting of renal venous flow before a significant increase in cardiac filling pressures is demonstrated and correlates with less diuretic efficiency.[74] Other renal hemodynamic parameters such as renal arterial resistive index and renal perfusion index, although showing correlation with CVP, mean arterial pressures, and effective renal plasma flow, have not extended to being predictors of clinical

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outcomes in CRS.[73] Renal ultrasonography provides information on chronicity of disease using renal size, echogenicity, cortical thickness, and abnormal corticomedullary ratios, which are helpful in identifying progression from type 1 CRS to a more indolent type 2 CRS phenotype or establishing AKI or CKD as the primary perturbation in the clinical presentation of CRS.[75]

Uremic cardiomyopathy evolves through the course of progression of CKD, with subtle alterations in cardiac structure occurring even before a clinically significant decline in renal function.[76] Speckle echocardiography with strain analysis allows a more detailed analysis of myocardial systolic function in the setting of normal LVEF and may have additive value over echocardiographic assessment of EF, including in uremic cardiomyopathy (type 4 CRS).[77] In a study of 40 control subjects and 90 patients with CKD across a range of eGFR, LV longitudinal systolic strain and early and late diastolic strain rates were significantly reduced in patients with CKD (–16.9±3.8%, 1.6±0.5%, and 1.3±0.4% in patients with CKD versus –22.5±0.6%, 2.3±0.2%, and 1.9±0.1% in control subjects; $P<0.001$ for all), despite overall preservation of EF.[78] Krishnasamy et al[79] demonstrated that global longitudinal strain was a significant predictor of all-cause mortality in CKD (HR, 1.08 [95% CI, 1.01–1.15]) in a single-center experience with 447 subjects.

Cardiac magnetic resonance imaging is the standard noninvasive method of assessing ventricular dimensions and function and fibrosis. Myocardial fibrosis in patients with uremic cardiomyopathy (type 4 CRS) occurs through multiple mechanisms not uniquely related to coronary artery disease. Early attempts to characterize and quantify myocardial fibrosis in ESKD with gadolinium-enhanced cardiac magnetic resonance imaging described a high prevalence of late gadolinium enhancement characteristic of coronary artery disease but also described a noninfarct pattern typical of more diffuse fibrosis.[76] The limitations in the use of gadolinium in advanced CKD resulting from the risk of nephrogenic systemic fibrosis were overcome in 2 recent studies that described prolonged native T1 relaxation time and abnormal global longitudinal strain in patients with prevalent HFpEF undergoing hemodialysis compared with control subjects.[80,81] The validation of non–gadolinium-based cardiac magnetic resonance in advanced CKD opens new possibilities in identifying subclinical LV dysfunction and has high potential as a tool for future studies in characterizing cardiac structure in future cardiorenal studies.

Volume Status Determination Strategies in CRS

Fluid overload represents a core target for treatment in the process of optimizing the vicious cycle of CRS. However, the optimal method to assess fluid status and to determine dry weight and appropriate decongestion in decompensated HF or kidney disease remains an unresolved issue. This section describes the role of several modalities available in conjunction with clinical assessment of volume status.

Bioimpedance Vector Analysis

Bioimpedance vector analysis (BIVA) is a noninvasive bedside volume assessment technique based on the electric principle that the body is a circuit with a given resistance (opposition of current flow through intracellular and extracellular solutions) and reactance (the capacitance of cells to store energy). With BIVA, total body water may be measured by placing a pair of electrodes on the dorsum of the wrist and ipsilateral ankle and then applying a 50-kHz current to the body. BIVA is displayed graphically so that relative hydration is depicted as vector length. Shorter vectors are associated with volume overload, whereas longer vectors equate to volume depletion (Figure 2). BIVA has shown promising results in distinguishing dyspnea caused by HF from other causes in patients presenting to the emergency department.[82,83] BIVA has also been combined with BNP to guide discharge timing in patients with AHF,[84] preventing AKI in the setting of high-dose diuretics for HF,[85] and prognosticating patients with high risk of rehospitalization and cardiovascular mortality.[86,87] In a recent study using a body composition analysis based on bioimpedance, a derived measure of fluid overload was found to be a key management parameter associated with mortality on both the low and high ends of the measurement.[88]

Measurement of IAP

In advanced HF, inefficient natriuresis with progressive volume overload may ultimately lead to a state of systemic congestion with increased IAP if the capacitance function of the splanchnic vasculature is insufficient.[24] In 60% of patients admitted with AHF, measurements of IAP are elevated beyond the baseline value range of 5 to 7 mm Hg.[24] Bedside noninvasive measurements of IAP can be obtained with a urinary bladder catheter connected to a transducer. Reversing increased IAP by decongestive therapy ameliorates serum creatinine in this setting, presumably by alleviating abdominal congestion.[89]

Relative Blood Volume Monitoring Devices

Devices that monitor relative blood volume have generated interest in optimizing volume status in decompensated HF. Radiolabeled albumin tracer injections (BVA-100, Daxor) are commercially available as a measuring tool for intravascular blood volume. A wide range of total blood volume values were reported in a small cohort of patients hospitalized with AHF, with marginally reduced intravascular volume after diuretic therapy despite large reductions in body weight.[90] It is unknown

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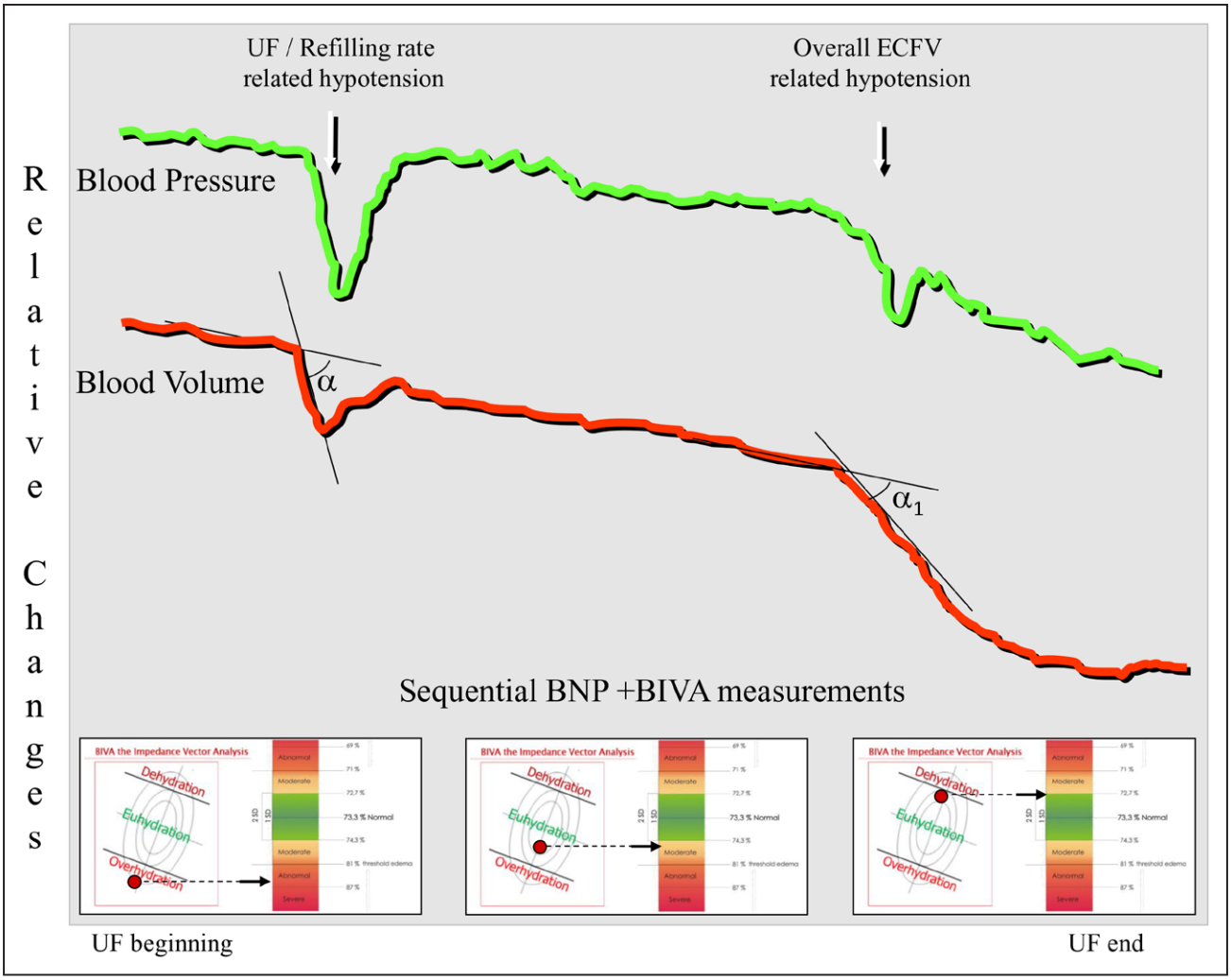

Figure 2. Bioimpedance vector analysis (BIVA) in a patient undergoing ultrafiltration (UF).
Relative hydration status is determined by the net vector of resistance to an applied current and reactance. Results from BIVA are compared with measurements made in healthy reference populations and are plotted as ellipses corresponding to the 50th, 75th, and 90th percentiles. Phase angle corresponds to the portion of electric current that is stored and subsequently released in a different phase and depends on cell integrity, cell membrane permeability, and total body water. BNP indicates B-type natriuretic peptide; and ECFV, extracellular fluid volume.

whether the addition of blood volume measurement devices will affect clinical outcomes in patients with AHF in the context of CRS.

Implantable Hemodynamic Monitoring Devices

The CHAMPION trial (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) demonstrated a lower hospitalization rate (HR, 0.72 [95% CI, 0.59–0.88]) and a trend toward lower mortality (HR, 0.68 [95% CI, 0.45–1.02]) in 456 patients with HF with reduced ejection fraction (HFrEF) in the group who received PA pressure–guided HF management versus control subjects.[91] Mean baseline eGFR in this study was 61.1±22.8 mL/min per 1.73 m^2 for the study group and 62.3±23.4 mL/min per 1.73 m^2 for the control group (P=0.69). The hospitalization reduction and survival benefit were amplified by increasing the application of guideline-directed medical therapy. Currently, data on the efficacy of this device in patients with CRS or HF with advanced CKD are lacking.

An implantable device (Optivol, Medtronic) has been used to assess transthoracic impedance as a measure of pulmonary fluid status.[92] Direct measurements of intrathoracic impedance with an implanted device have been shown to have prognostic value in HF.[93] However, a reduction in outpatient visits for HF symptoms or hospital admissions with the use of device alerts has not been demonstrated.[94,95] Specific data on outcomes with CRS using implantable intrathoracic impedance measurements are currently lacking.

Invasive Hemodynamic Monitoring in CRS

Routine evaluation of invasive hemodynamics has not been recommended in AHF because the ESCAPE trial did not show a reduction in either mortality or rehospitalizations with such a strategy in patients with equipoise for right-sided heart catheterization.[96] A post hoc

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analysis of the ESCAPE trial showed that a PA catheter–guided strategy was associated with less average increase in creatinine but did not decrease the incidence of defined worsening renal impairment during hospitalization or affect renal function after discharge relative to clinical assessment alone.[22] Nevertheless, PA catheterization might still be warranted in patients with CRS who are difficult to treat, aiming to identify and treat subclinical congestion while avoiding intravascular underfilling and modulating hemodynamics to improve dual organ function. Common relevant scenarios include underdiagnosis of culprit hemodynamic contributors such as pulmonary hypertension (PH) or cardiogenic shock, underestimation of valvular dysfunction such as mitral regurgitation or tricuspid regurgitation, and accurate assessment of volume overload or RV failure. The RA/pulmonary capillary wedge pressure ratio, reflecting a disproportionate increase in RV to LV pressures, is inversely associated with eGFR in patients with AHF.[97] Notably, cardiorenal hemodynamic measurements as assessed by invasive catheterization are confounded by the presence of elevated IAP or ascites, which represents a clinical caveat when PA catheterization is used in the context of CRS.[24]

The relative successes and failures of adjuvant methods in assessing volume status and guiding diuresis or ultrafiltration goals depend on the degree of plasma refill in response to decongestive therapies. Sodium in the subcuticular and interstitial tissues, venous pressure, oncotic pressure, and several other poorly understood factors affect plasma refill rates with diuresis and ultrafiltration.[98,99] ^{23}Na-labeled magnetic resonance imaging has demonstrated Na^+ in muscle and skin in patients with HF, and diuretic and ultrafiltration treatments can mobilize this Na^+ deposition in varying rates.[99,100] Thus, attempts at optimizing congestion in CRS with adjunct volume measurement techniques must factor in the limitations with predicting plasma refill rate with these devices, as well as the practical constraints of implementing clinically driven protocols based on theoretical extrapolations of volume assessment.

TREATMENT STRATEGIES IN CRS

Decongestive Therapies

Diuretics

Fluid retention and congestion are hallmarks of AHF, and diuretics are a cornerstone of the management in patients with or without CRS. Diuretics are commonly prescribed (≈90% of patients with AHF),[101] but unlike many other pharmacological therapies for HF that are supported by data from large clinical trials, evidence-based best clinical practices for diuretic use in HF remain uncertain, affording immediate relief of HF symptoms but no benefit in short- or long-term mortality or rehospitalization.[102,103] The AHA and others recently endorsed diuretic use in HF with a Class I recommendation based on expert opinion alone.[58] Diuretic therapy is also standard of care for subjects enrolled in interventional clinical trials for HF. Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid), named for their site of action in the loop of Henle of the nephron, represent the primary class of diuretics in HF. This section focuses on the effects of loop diuretics on renal hemodynamics and the physiology of diuretic resistance with relevance to CRS.

Kidney Injury (Type 1 CRS) and RAAS Activation in Association With Loop Diuretics

Loop diuretics inhibit the $Na^+K^+2Cl^-$ cotransporter in the thick ascending limb of the loop of Henle, and $Na^+K^+2Cl^-$ inhibition leads primarily to natriuresis and volume loss in edematous states such as HF. Loop diuretics have a short duration of action, lasting 2 to 3 hours and up to 6 hours for an intravenous bolus and oral administration, respectively. Oral furosemide has ≈50% bioavailability with a wide range of values,[104] explaining the variation in response to oral doses. Intravenous administration and novel subcutaneous infusions of furosemide ensure 100% bioavailability.[105,106] Torsemide has a longer half-life and thus requires less frequent dosing.[107] Given the more predictable oral bioavailability and longer half-life in patients with HF, torsemide may be more effective as a decongestive therapy compared with furosemide, as suggested by several small studies and a recent meta-analysis.[108–110]

Loop diuretics have multiple effects on neurohormonal activation and renal and systemic hemodynamics that can predispose to kidney injury. Worsening kidney function in AHF (type 1 CRS) is associated with higher rehospitalization rates and mortality,[111,112] and several studies have assessed the clinical benefit of different dosing protocols for loop diuretics in AHF and their effect on kidney function. The DOSE-AHF trial (Diuretic Optimization Strategies Evaluation in Acute Heart Failure) randomized 308 patients with AHF to bolus versus continuous infusions of furosemide and a low-dose (intravenous equivalent of patient's home diuretic dose) versus high-dose regimen (2.5 times the patient's home loop diuretic dose intravenously) in a 2-by-2 factorial design model.[113] In continuous versus intermittent diuretic dosing, no significant differences were observed in patients' symptoms (P=0.47) or change in renal function (P=0.45); that is, no significant differences in the incidence of type 1 CRS were seen. However there was a trend in favor of the high-dose strategy compared with the standard dose in symptom improvement (P=0.06), without a significant difference change in renal function (P=0.21). The DIUR-AHF trial (Loop Diuretic Therapy in Acutely Decompensated Heart Failure) randomized 92 patients

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with AHF to a bolus or continuous infusion strategy. Like the DOSE-AHF trial, there was no difference in mortality; however, the continuous infusion was associated with greater rates of hyponatremia and the need for vasopressor infusion, and at 6 months, there were higher rates in the composite of rehospitalization or death.[114] A post hoc analysis of 198 patients who developed type 1 CRS, pooled from 3 randomized clinical trials, DOSE-AHF, CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure), and ROSE-AHF (Renal Optimization Strategies Evaluation in Acute Heart Failure), compared a urine volume goal-directed stepwise diuretic algorithm and standard diuretic therapy. The stepwise algorithm aimed for a 24-hour urine volume between 3 and 4 L with furosemide with or without metolazone (a thiazide-type diuretic that inhibits sodium uptake in the downstream nephron segment) and showed more weight loss (−1.5±2.4 kg versus −0.4±1.5 kg; $P<0.001$) and higher net fluid loss (1.705±1.417 L versus 0.892±1.395 L; $P<0.001$) with an improvement in renal function (Δ serum creatinine, −0.1±0.3 mg/dL versus 0.0±0.03 mg/dL; $P=0.03$)[115] compared with standard diuretic therapy. ROSE-AHF specifically compared the effect of low-dose dopamine, nesiritide, or placebo on decongestion and renal function.[116] In an ancillary study of ROSE-AHF, investigators measured biomarkers of kidney injury in individuals taking high-dose furosemide. In this analysis, kidney tubular injury detected by biomarkers did not appear to have an association with worsening renal function in the context of aggressive diuresis of individuals with AHF. Of note, the mean baseline eGFR was 44 mL/min per 1.73 m^2, providing relevance for individuals with type 1 and 2 CRS.[9] Increases in NGAL, NAG (N-acetyl-β-D-glucosaminidase), and KIM-1 (kidney injury molecule-1) were paradoxically associated with improved survival (HR, 0.80 per 10-percentile increase [95% CI, 0.69–0.91]). These studies in AHF would suggest that loop diuretics per se may not contribute to biomarker-associated renal injury, and a decrease in the eGFR may be a surrogate for severity of cardiac disease. On the basis of the analyses highlighted above, high-dose intermittent furosemide appears to be safe and effective in AHF. Whether diuretics promote renal injury in individuals with more severe baseline kidney function, for example, stage 4 or 5 CKD, is uncertain. Furthermore, without guidance from assessment of blood volume, rate of plasma refill, or measures of acute tubular injury, it is apparent that the use of diuretics in HF is empirical without a proven strategy associated with favorable outcomes from either observational studies or randomized trials. This raises the hope for future trials guided by these parameters to improve outcomes compared with usual care.

The potentially deleterious effects of RAAS activation by loop diuretics could theoretically limit the ability to break the neurohormonal vicious cycle with AHF. However, in a follow-up analysis of DOSE-AHF and CARRESS-HF, high-dose loop diuretic therapy did not result in RAAS activation greater than that with low-dose diuretic therapy. In fact, ultrafiltration resulted in a greater increase in plasma renin activity than stepwise pharmacological care. Neither plasma renin activity nor aldosterone was significantly associated with short-term outcomes in AHF and CRS.[117] This emphasizes the key concept that blood volume represents a small component of extracellular volume from which fluid losses are mobilized in the short term by diuretics or ultrafiltration. Reductions in extracellular fluid volume are further limited by the degree of plasma refill from the extracellular fluid into the intravascular space, the impairment of which further triggers endogenous production of hormones such as angiotensin II and vasopressin. Thus, a careful clinical assessment of the degree of plasma refill is critical in minimizing triggering of the adaptive neurohormonal responses to impaired plasma refill when decongestive therapies are administered.

Diuretic Resistance

Diuretic resistance is defined as the attenuation of the maximal diuretic effect that ultimately limits sodium and chloride excretion and is a well-characterized phenomenon of diuretic use. In contrast to the lack of kidney injury associated with diuretic use,[9] diuretic resistance is associated with renal impairment, increased risk of rehospitalization after HF, and mortality.[118,119]

Several factors contribute to diuretic resistance, including drug pharmacokinetics and pharmacodynamics, the braking phenomenon, and tubular remodeling (Figure 3). Free, unbound loop diuretics must reach the urinary lumen of the thick ascending limb and bind to the site of chloride entry to inhibit $Na^+K^+2Cl^-$. Therefore, for outpatient therapy, oral bioavailability is the first line of resistance. All loop diuretics are not created equal. Bumetanide and torsemide have higher bioavailability than furosemide.[120] HF and food intake can prolong time to peak concentration and the peak drug levels.[121] Because loop diuretics are 95% protein bound, hypoalbuminemia increases the volume of distribution and reduces the availability of loop diuretics for facilitated diffusion. Nonsteroidal anti-inflammatory drugs and uremic toxins can also competitively inhibit drug transport across proximal tubular epithelial cells.

Specific factors related to CRS promote diuretic resistance. The bioavailability of loop diuretics is similar, but CKD reduces excretion of diuretic into the tubular lumen. CKD does not limit the peak effect of drug delivered to the lumen. Overall diuretic-induced sodium excretion is reduced in CKD by the reduced and diminished filtered load of sodium. Thus, administration of effective doses multiple times per day can circumvent the above constraints.[122,123] HF also reduces

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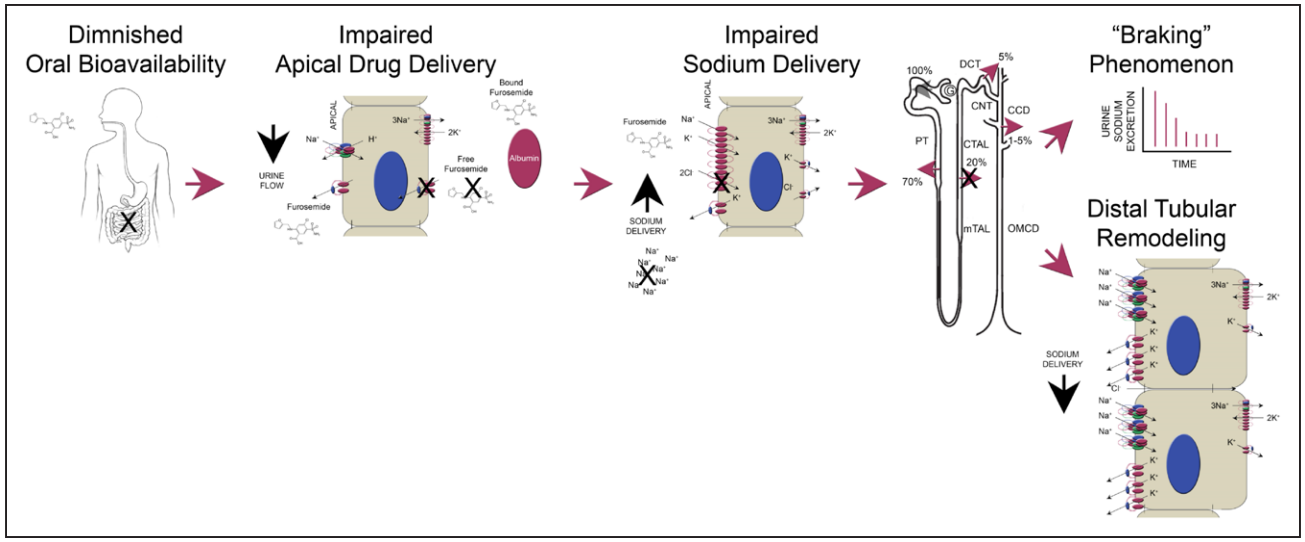

Figure 3. Mechanisms of diuretic resistance in cardiorenal syndrome.
Several extrarenal and renal factors impede the delivery of diuretic to the site of action in the nephron. After initial efficacy, diuretics become less effective because of the braking phenomenon and distal tubular remodeling. Potential strategies to overcome diuretic resistance include increased dose, frequency, and combination diuretic therapy. CCD indicates cortical collecting duct; CNT, connecting tubule; cTAL, cortical thick ascending limb; DCT, distal convoluted tubule; mTAL, medullary thick ascending limb; OMCD, outer medullary collecting duct; and PT, proximal tubule.

the peak effect of the drug, which may be caused by increased proximal reabsorption of sodium (eg, resulting from RAAS activation) or increased expression of $Na^+K^+2Cl^-$.[124] These changes necessitate more frequent dosing rather than dose escalation to achieve maximal sodium excretion.

Diuretic use (eg, in chronic HF and in type 1 or 2 CRS) can induce the braking phenomenon in the short term and distal tubular hypertrophy in the long term. The braking phenomenon refers to diminished diuretic efficacy with each successive dose. The effect is observed within hours, but the mechanism is unclear. Sodium loss is thought to play a role in the upregulation of proximal and distal sodium transporters, and sodium repletion can attenuate this compensation[125] and, in turn, the braking phenomenon. A recent study including indexes of proximal versus sodium reabsorption in subjects with HF treated with furosemide indicates that enhanced distal sodium transport, more than proximal transport, attenuates the maximal efficacy of furosemide.[126] This nephron-specific element of diuretic resistance is also more consequential than delivery of the loop diuretic to the site of action[127] and forms the rationale for use of thiazide-type diuretics to augment furosemide-induced sodium excretion. Whether the concept of diuretic synergy can be transferred to HF and to CRS is uncertain. A large-scale randomized clinical trial of thiazide-type diuretics as an adjunct to furosemide in HF or CRS is lacking. However, the ATHENA-HF trial (Efficacy and Safety of Spironolactone in Acute Heart Failure) tested spironolactone, a potassium-sparing diuretic that targets another hypertrophied downstream nephron segment, versus placebo and did not demonstrate significant clinical benefit.[128] Recent data suggest that hypochloremia plays a critical role in neurohormonal activation in patients with HF on high-dose loop diuretics, which may contribute to diuretic resistance in these subjects.[129]

Diuretic Efficiency

The concept of diuretic efficiency focuses on quantifying the renal response to a fixed dose of a loop diuretic using net fluid output in milliliters or weight change in kilogram per 40 mg furosemide equivalent[130] or natriuretic response to continuous intravenous furosemide defined as urine sodium to urine furosemide ratio.[131] Diuretic efficiency may serve as a prognostic marker in CRS. Patients with diuretic efficiency below the median in the ESCAPE trial experienced nearly 3 times the risk of death compared with those patients with diuretic efficiency above the median, despite adjustment for baseline and in-hospital characteristics (HR, 2.86 [95% CI, 1.53–5.36]).[130] As another measure of diuretic efficiency, Singh et al[131] measured the ratios of urine sodium to urine furosemide in 52 patients hospitalized with AHF on continuous furosemide infusions. Patients with a ratio of urine sodium to urine furosemide <2 mmol/mg (indicative of low diuretic efficiency) experienced less weight loss and fluid removal in the first 24 hours and were at significantly increased risk for death, HF rehospitalization, and cardiac transplantation in an adjusted multivariate analysis (HR, 2.2 [95% CI, 1.08–4.49]). In addition, these patients were more likely to experience worsening renal function in the context of decongestive therapies. Thus, measurements of diuretic efficiency may help to identify individuals who develop diuretic resistance and to identify a higher-risk subset of patients with CRS with worse outcomes. Further stud-

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ies on the utility of diuretic efficiency in guiding targeted treatment strategies in CRS are necessary.

Ultrafiltration

Ultrafiltration, achieved by passing blood through hollow fibers made of semipermeable material while applying a negative pressure to the space surrounding the fibers, causes isotonic fluid to be removed from the intravascular space. The composition of ultrafiltrate contrasts with the much lower sodium content in the urine produced by loop diuretics[132] and allows decongestion without the use of loop diuretics, with potential benefits including less potassium wasting, less renin and aldosterone release, and increased sodium loss. Thus, the optimal mode of decongestion in AHF using diuresis versus ultrafiltration has been the subject of clinical trials, and key aspects of the randomized trials in this field are summarized in Table 3.

The UNLOAD trial (Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure) randomized 200 patients within 24 hours of hospitalization for AHF to either loop diuretics or ultrafiltration.[134] The primary end of weight loss at 48 hours was significantly higher in the ultrafiltration group (5.0±0.68 kg versus 3.1±0.75 kg; *P*=0.001), whereas dyspnea scores between the groups were not significantly different. There was a significant reduction in 90-day rehospitalization rates in the ultrafiltration arm, a secondary end point. Although UNLOAD demonstrated no differences in episodes of hypotension within the first 48 hours or serum creatinine at 90 days between the 2 groups, it was unclear whether the secondary outcome of reduced readmissions at 90 days could have been achieved in the diuretic arm with more aggressive dose escalation.

CARRESS-HF was a landmark study that enrolled 188 patients admitted with AHF and worsening renal function.[135] Of all randomized trials for ultrafiltration in AHF, CARRESS-HF represents the only study that included patients with type 1 CRS. The primary end point was a bivariate change in weight and creatinine at 96 hours after randomization. No significant differences in weight loss were noted between the 2 groups (5.5±5.1 kg in the diuretic group versus 5.7±3.9 kg in the ultrafiltration group; *P*=0.58). The ultrafiltration group had an increase in serum creatinine of 0.23 mg/dL versus a decrease of 0.04±0.53 mg/dL in the diuretic group (*P*=0.003). In addition, the patients in the ultrafiltration group experienced a higher rate of adverse events (72% versus 53%; *P*=0.03).

The contrasting results between CARRESS-HF and UNLOAD highlight the nuances in study design, patient selection, and therapeutic algorithms unique to each study. Patients in CARRESS-HF had to demonstrate worsening renal function (CRS) to qualify for inclusion, signifying a sicker group of patients. In addition, ultrafiltration protocols were at fixed rates in CARRESS-HF, which physiologically contrast the documented decrease in plasma refill rates with continuous ultrafiltration.[138] The glomerular filtration and tubular secretion of creatinine with diuresis differ from removal of creatinine with ultrafiltration with a sieving coefficient of 1 and may not represent the actual effects of either therapy on renal function. Despite these issues, CARRESS-HF provided a strong argument against the use of ultrafiltration as primary treatment in patients with type 1 CRS. The AVOID-HF trial (Aquapheresis Versus Intravenous Diuretics Hospitalizations for Heart Failure), which sought to address these criticisms with a stepped-up diuretic algorithm and a detailed ultrafiltration protocol, was terminated before completion because of slow enrollment.[137] In the 224 patients who completed the protocol, nonsignificant trends toward reduced HF readmissions at 90 days were achieved, but an increase in adverse events was also reported in the ultrafiltration group (14.6% versus 5.4%; *P*=0.026). Future studies that address the utility of ultrafiltration in patients with functional diuretic resistance and frequent readmission for AHF are necessary to see whether clinically and economically meaningful outcomes can be achieved in these high-risk populations.

Neurohormonal Modulation and Vasodilator and Inotropic Therapy

The maladaptive neurohumoral responses in AHF resulting from type 1 CRS involve key vasoactive peptides such as vasopressin, endothelin, and adenosine and a diminished response to endogenous natriuretic peptides. In addition, the hemodynamic compromise that often accompanies HF may contribute to type 1 CRS. This section reviews pharmacological agents that affect neurohormones or improve hemodynamics that have been studied in the treatment of CRS.

Arginine vasopressin is a nonapeptide hormone released by posterior pituitary and in conditions of elevated serum osmolarity, reduced cardiac index, or hypovolemia.[139] Tolvaptan, a selective V2 receptor antagonist, causes aquaresis without loss of sodium. The EVEREST program (Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study With Tolvaptan) evaluated the use of tolvaptan in AHF and LVEF <40% and showed similar rates of adverse events in the tolvaptan and placebo groups with greater degrees of weight reduction in the tolvaptan arm in 2 short-term trials.[140] No benefits in reduction in death or the composite of cardiovascular death and HHF were noted in the long-term trial.[141] In TACTICS-HF (Targeting Acute Congestion With Tolvaptan in Congestive Heart Failure), the addition of tolvaptan to a standardized furosemide regimen did not improve the number of responders at 24 hours despite greater weight loss.[142] Similarly, the

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Table 3. Evidence Table of RCTs Comparing Pharmacological Therapy for Fluid Overload and Ultrafiltration in Patients With Acute Decompensated HF

Study	Subjects, n	Primary End Point	UF Protocol	Diuretics Protocol	Effect on Renal Function	Effect on Weight Loss	Adverse Events
RAPID-CHF[133]	40	Weight loss at 24 h	Single 8-h UF session to maximum rate of 500 mL/min per 1.73 m^2	Clinician based	NS	Similar in both groups; trend toward higher weight loss in UF arm	…
UNLOAD[134]	200	Weight loss and dyspnea at 48 h	Time and rate of UF flexible; maximum rate of 500 mL/min per 1.73 m^2	Clinician based	NS	UF>DT	…
CARRESS-HF[135]	188	Change in SCr and weight at 96 h	Fixed UF rate of 200 mL/min per 1.73 m^2	Prespecified stepped-up algorithm	Significant increase in SCr with UF	Similar in both groups	Higher SAEs in UF arm
CUORE[136]	56	Hospitalization for HF at 1 y	Time and rate of UF flexible; maximum rate of 500 mL/min per 1.73 m^2	Clinician based	Significant increase in SCr with DT at 6 mo	Similar in both groups	…
AVOID-HF*[137]	224	Time to HF <90 d after discharge	Time and rate of UF flexible; maximum rate of 500 mL/min per 1.73 m^2	Prespecified algorithm	NS	Similar in both groups	Higher SAEs in UF arm

AVOID-HF indicates Aquapheresis Versus Intravenous Diuretics Hospitalizations for Heart Failure; CARRESS-HF, Cardiorenal Rescue Study in Acute Decompensated Heart Failure; CUORE, Continuous Ultrafiltration for Congestive Heart Failure; DT, diuretic therapy; ellipses (…), data not available or reported.; HF, heart failure; NS, not significant; RAPID-CHF, Relief for Acutely Fluid Overloaded Patients With Decompensated Congestive Heart Failure; RCT, randomized controlled trial; SAE, serious adverse event; SCr, serum creatinine; UF, ultrafiltration; and UNLOAD, Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure.

*Trial terminated early. Data as reported on subjects enrolled until trial termination.

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SECRET of CHF trial (Short Term Clinical Effects of Tolvaptan in Patients Hospitalized for Worsening Heart Failure With Challenging Volume Management) trial did not show significant improvement in dyspnea in patients with AHF who were selected for greater potential benefit from tolvaptan.[143]

Although patients with AHF have elevated natriuretic peptides, the vasodilatory and natriuretic effects of the endogenous release of these substances are often not enough to overcome the hemodynamic effects of the other neurohormones mentioned. Nesiritide is a recombinant BNP with venous, arterial, and coronary vasodilatory properties that reduce afterload and increase CO without inotropic effects. It also causes natriuresis, improves the GFR, and suppresses the RAAS axis.[144,145] The ASCEND-HF trial (Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure) randomized 7141 patients with AHF to 1 to 7 days of intravenous nesiritide or placebo. The primary end point of dyspnea improvement, rehospitalization, or death was not statistically different between groups. The coprimary end point of dyspnea improvement at 6 and 24 hours was statistically higher in the nesiritide group, but this group also had more hypotension, and there were no differences in renal function.[146] The ROSE-AHF trial randomized 360 patients with AHF independent of LVEF and eGFR of 15 to 60 mL/min per 1.73 m^2 at 1:1 to low-dose nesiritide or dopamine and, within each randomization, randomized them further at 2:1 into either active treatment or placebo infusions for 72 hours. Low-dose nesiritide had no significant effect on the coprimary end points of cumulative urine volume and change in serum CysC at 72 hours and no effect on the secondary end points reflective of decongestion, renal function, or clinical outcomes.[116]

Although theoretically attractive, neurohormonal modulation in the AHF setting has failed to improve hard clinical and renal end points in large randomized studies. Because of this, only tolvaptan and nesiritide have been approved for use by the US Food and Drug Administration, and their use is limited to specific clinical situations.

Inotropes have the potential to improve type 1 CRS by improving CO and reducing venous congestion. Specific inotropes such as dopamine have direct renal effects that may additionally result in improvement of type 1 CRS, but clinical data are mixed. A common theme in studies of inotropic therapy for AHF and reduced EF is that although favorable acute hemodynamic effects are achieved, long-term cardiovascular outcomes are not affected because of the presence of arrhythmias, ischemia, and worsening long-term myocardial function.[147]

Dopamine is a catecholamine with effects on the β- and α-adrenergic receptors, as well as the renal dopaminergic receptors, resulting in cardiac inotropy, systemic vasoconstriction, and improved renal blood flow.[148] Early studies supported the renal protective effects of low-dose

dopamine; however, subsequent studies demonstrated a lack of long-term clinical improvement in the treatment of AHF. Meta-analysis data have demonstrated improved urine output but no significant difference in change in creatinine, rehospitalization, or mortality with low-dose dobutamine used in various clinical scenarios.[149] As discussed, the ROSE-AHF trial showed no difference in the coprimary end points of cumulative urine volume and change in serum CysC at 72 hours or any effect on the secondary end points reflective of decongestion, renal function, or clinical outcomes when a 72-hour infusion of low-dose dopamine was compared with placebo in patients with AHF.[116] Post hoc analysis demonstrated a differential effect on 72-hour cumulative urine volume in favor of dopamine in patients with LVEF ≤40% (P=0.029) compared with nesiritide in patients with LVEF >40% (P=0.001) but no differential effect in change in CysC (P=0.66), suggesting a worse clinical effect of low-dose dopamine in patients with HFpEF.[150] Other novel inotropes such as levosimendan (calcium-sensitizing agent and potassium channel modulator) and omecamptiv mecarbil (cardiac myosin activators) have limited data in the context of CRS.

Although progress has been made in the field of inotrope and vasodilator therapy, its long-term efficacy in the treatment of AHF and type 1 CRS is yet to be demonstrated.

RAAS Inhibition in Chronic CRS

Angiotensin-Converting Enzyme Inhibitors/ARBs

Although the importance of RAAS inhibition in slowing CKD progression is well established, there is a paucity of data on clinically relevant long-term renal end points in trials on RAAS inhibition in HF. Given the known hemodynamic (and potentially reversible) effects of angiotensin blockade, interpreting fluctuations in serum creatinine as meaningful renal end points in the context of the use of angiotensin-converting enzyme (ACE) inhibitors and ARBs poses challenges in clinical practice. The benefits of ACE inhibitors in patients with HF and renal impairment have been demonstrated in observational data[151,152] and post hoc analyses of randomized controlled trials (RCTs). These studies pertain specifically to the presence of preexisting renal impairment (type 2 or 4 CRS) in outpatient studies with HF, not to acutely decompensated subjects with CRS.

CONSENSUS demonstrated a marked reduction in HF-associated mortality and symptom burden and was characterized by a doubling of serum creatinine in 11% of subjects taking enalapril compared with those taking placebo[153] However, trends in serum creatinine rise were predominantly early and returned to within 30% of baseline values in most subjects, consistent with the known hemodynamic effects of ACE inhibitors, with the effect of concomitant diuretic use and hypotension being independent predictors of doubling of serum creatinine.[21] SOLVD (Study of Left Ventricular Dysfunction) reiterated the benefits of enalapril for HF symptoms and hospitalization reduction (LVEF <35%, serum creatinine <2.5 mg/dL) in a much larger population compared with CONSENSUS (2569 versus 253 subjects).[154] The enalapril group in SOLVD showed a 33% higher likelihood of a serum creatinine rise of >0.5 mg/dL, but no data on progression of CKD, ESKD, or doubling of creatinine were reported. A post hoc analysis of SOLVD with HF and CKD demonstrated the mortality benefits even in subjects with higher degrees of CKD.[155] The overall incidence of hyperkalemia was 6% overall with enalapril, correlating with the severity of renal dysfunction.[156] However, in a meta-analysis of 5 placebo-controlled RCTs of ACE inhibitors in HF by Flather et al,[157] drug discontinuation was rarely necessary despite higher rates of AKI in the treatment arms versus placebo in most cases. A meta-analysis of 8 trials looking at the use of RAAS inhibition in KT demonstrated a higher risk of hyperkalemia (relative risk [RR], 2.44 [95% CI, 1.53–3.9]).[158] The strength of evidence of ACE inhibitors in HF with predialytic CKD is not established given the lack of inclusion of these patients in RCTs for HF. Hospitalization and safety reporting data from the ongoing multicenter randomized controlled STOP-ACEi trial (Trial of Angiotensin-Converting Enzyme Inhibitor/Angiotensin Receptor Blocker Withdrawal in Advanced Renal Disease; ISRCTN62869767) will shed light on the consequences of ACE inhibitors in advanced CKD and related cardiorenal outcomes. Although data on ARBs in CKD and HF specifically are sparse, in a propensity score analysis of 1665 patients with HF (EF <45%) and eGFR <60 mL/min per 1.73 m^2, treatment with an ACE inhibitor or ARB was associated with significant reductions in all-cause mortality (HR, 0.68 [95% CI, 0.74–0.996]; P=0.04)[159] (Tables 4 and 5). The addition of ARBs to ACE inhibitors has been discouraged because of the increased risk of adverse events.[176]

Neprilysin/Renin-Angiotensin Inhibitors

Trials that looked at outcomes with the combination of renin angiotensin system blocker/neprilysin inhibition (sacubitril/valsartan and omapatrilat) provided an excellent opportunity to study the combined approach to RAAS blockade and vasodilator versus RAAS blockade alone. A recent meta-analysis analyzed data from 3 trials in HFrEF that compared combined neprilysin/RAAS inhibition with RAAS inhibition alone and included the following: IMPRESS (Inhibition of Metallo Protease by Omapatrilat in a Randomized Exercise and Symptoms Study of Heart Failure; n=573), OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events trial; n=5770), and PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; n=8399).[177] The composite outcome of death or HHF was reduced numerically in patients receiving

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Table 4. Evidence Table of Outcomes in HF in Subjects With CKD Treated With ACE Inhibitors

Study	n	Study Design	Population	CKD	Concomitant Therapy	Baseline Renal Function	Outcome in CKD Group
CONSENSUS[160–162]	235	RCT, enalapril vs placebo	Patients with NYHA class IV HF	Excluded: GFR <30 mL/min per 1.73 m^2 CKD: 55% have Cr >1.58 mg/dL	MRA 42% Digoxin 93% β-Blocker 3%	Cr 1.45 mg/dL GFR ≈47 mL/min per 1.73 m^2	Mortality: NS
SOLVD Treatment[154,163]	2569	RCT, enalapril vs placebo	HFrEF, EF ≤35%, symptomatic HF	Excluded: Cr >2.5mg/dL CKD: CKD ≥3A (41%) CKD ≥3B (10%)	MRA 9% Digoxin 67% β-Blocker 8%	Cr 1.2 mg/dL	Mortality: CKD ≥2: NS HR, 0.88 (95% CI, 0.73–1.06) CKD ≥3B: NS HR, 0.76 (95% CI, 0.54–1.08) HHF: CKD ≥3A: HR, 0.59 (95% CI, 0.48–0.73) CKD ≥3B: HR, 0.69 (95% CI, 0.46–1.02)
SOLVD Prevention[164]	4228	RCT, enalapril vs placebo	LV dysfunction EF ≤35%, NYHA class I/II	Excluded: Cr >2.0 mg/dL	MRA 4% Digoxin 12% β-Blocker 35%	Cr 1.2 mg/dL	No CKD analysis
SAVE[165,166]	2183	RCT, captopril vs placebo	MI with LV dysfunction EF 31%	Excluded: Cr ≥2.5 mg/dL CKD: GFR ≥75 mL/min per 1.73 m^2: 37% GFR 75–60 mL/min per 1.73 m^2: 30% CKD3A: 24% CKD ≥3B: 9%	β-Blocker 35%	Cr 1.3 mg/dL	Mortality: HR, 0.79 (95% CI, 0.65–0.95) HF: HR, 0.69 (95% CI, 0.57–0.84) No subgroup HR in CKD NNT for MI, cardiovascular death, or HF: CKD vs non-CKD=9 vs 19
ATLAS[167]	3164; 405 not previously on ACE inhibitor	RCT, lisinopril high dose vs low dose	Symptomatic HF, EF ≤30%	Excluded: Cr 2.5 mg/dL CKD: Cr >1.5 31%	β-Blocker 11% Digoxin 67%	Cr 1.3 mg/dL	Adverse event in CKD: high dose vs low dose Hypotension: 31% vs 21.4% Renal dysfunction/hyperkalemia: 15.7% vs 10%
DIG Database[168]	1707 patients with CKD from DIG data set, 208 after match	Propensity score analysis of DIG trial data, ACE inhibitor vs no ACE inhibitor	Chronic HF with sinus rhythm, mean EF 28%	Excluded: Cr ≥2.5 mg/dL CKD: Cr ≥1.5mg/dL for men and ≥1.3 mg/dL for women	Digoxin 47% MRA 12%	Cr 1.8 mg/dL GFR 40 mL/min per 1.73 m^2	All-cause mortality Not matched, adjusted: HR, 0.66 (95% CI, 0.49–0.90) Matched, adjusted: 0.58 (95% CI, 0.35–0.96)
Berger et al[169]	4573	Retrospective, ACE inhibitor or ARB vs no ACE inhibitor or ARB	Patients with CHF (Framingham criteria) with CKD	CKD: CKD1: 22% CKD2: 25% CKD3: 37% CKD4: 11% CKD5: 7%	β-Blocker 50% MRA 20%	NA	All-cause mortality: ACE inhibitor/ARB vs no ACE inhibitor Nondialysis CKD: 11% vs 41%, *P*=0.05 CKD2: 6.3% vs 8.6% CKD3: 5.4% vs 14% CKD4: 9.4% vs 18.5%
Ahmed et al[170]	1340	Retrospective, propensity-matched analysis, ACE inhibitor/ARB vs no ACE inhibitor/ARB	HFpEF with CKD	CKD: CKD ≥3 100%	β-Blocker 20% MRA 10%	Cr 1.7 mg/dL GFR 40 mL/min per 1.73 m^2	All-cause mortality: Not matched, adjusted: HR, 0.83 (95% CI, 0.72–0.96) Matched: HR, 0.82 (95% CI, 0.70–0.97)

(*Continued*)

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Table 4. Continued

Study	n	Study Design	Population	CKD	Concomitant Therapy	Baseline Renal Function	Outcome in CKD Group
Edner et al[171]	2410	Prospective, propensity-matched analysis, ACE inhibitor (67%)/ARB (31%)/ both 2% vs no ACE inhibitor/ARB	HFrEF, EF ≤39% with CKD4	CKD ≥4: 100%	β-Blocker 87% MRA 25% Digoxin 11%	GFR 23 mL/ min per 1.73 m^2	All-cause mortality: Matched adjusted: HR, 0.83 (95% CI, 0.73–0.94) Overall adjusted: HR, 0.81 (95% CI, 0.73–0.91)
Gurwitz et al[172]	2414	HFrEF and HFpEF with chronic lung disease and CKD	HFrEF 32% HFpEF 68%	GFR <60 mL/min per 1.73 m^2	NA	NA	HFrEF: All-cause mortality: HR, 0.6 (95% CI, 0.4–0.9) HHF: HR, 0.43 (95% CI, 0.28–0.67) HFpEF: All-cause mortality: HR, 0.5 (95% CI, 0.3–0.8) HHF: HR, 0.35 (95% CI, 0.18–0.68)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ATLAS, Assessment of Treatment With Lisinopril and Survival; CHF, congestive heart failure; CKD, chronic kidney disease; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; Cr, creatinine; DIG, Digitalis Investigation Group; EF, ejection fraction; GFR, glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reserved ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; LV, left ventricular; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NA, not applicable; NNT, number needed to treat; NS, not significant; NYHA, New York Heart Association; RCT, randomized controlled trial; SAVE, Survival and Ventricular Enlargement; and SOLVD, Study of Left Ventricular Dysfunction.

combined neprilysin/RAAS inhibition in all 3 trials, with a pooled HR of 0.86 (95% CI, 0.76–0.97; *P*=0.013). Combined neprilysin/RAAS inhibition compared with ACE inhibitor was associated with more hypotension but less renal dysfunction and hyperkalemia in all 3 trials. In the PARAMOUNT trial (Prospective Comparison of ARNI Versus ARB on Management of Heart Failure With Preserved Ejection Fraction), LCZ696 reduced NT-proBNP, blood pressure, and atrial size to a greater extent while preserving eGFR to a greater extent (36-week decline of GFR, 1.6 mL/min per 1.73 m^2 in the LCZ696 group versus 5.2 mL/min per 1.73 m^2 in the valsartan group; *P*=0.007).[178] In a subset analysis of PARADIGM-HF, treatment with sacubitril/valsartan resulted a slower rate of decrease in eGFR compared with enalapril, including in patients with CKD, despite a modest increased in albuminuria.[179] The HARP-III trial (UK Heart and Renal Protection III), which is a multicenter double-blind RCT comparing 97/103 mg of sacubitril/valsartan (2 times daily) with 300 mg of irbesartan (1 time daily) among 414 patients with CKD, will be the first test of an angiotensin receptor neprilysin inhibitor in patients with CKD with or without proteinuria.[180]

Mineralocorticoid Receptor Antagonists

The long-term efficacy of achieving complete suppression of RAAS with an ACE inhibitor/ARB is limited by the phenomenon of aldosterone escape, resulting in an increased level of serum aldosterone. Mineralocorticoid receptor antagonists (MRAs), when added to an ACE inhibitor/ARB, can provide more suppression of RAAS with potential long-term cardiorenal benefits. The reduction in mortality and cardiovascular events with HFrEF was demonstrated in RALES (Randomized Aldactone Evaluation Study)[181] and EPHESUS (Eplerenone in Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival).[182] In the EMPHASIS-HF trial (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), in which 33% of patients had an eGFR <60 mL/min per 1.73 m^2, the effect of eplerenone on the primary composite end point on HHF or cardiovascular death was consistent in patients dichotomized at an eGFR <60 mL/min per 1.73 m^2.[183] Data on the safety and efficacy of MRAs in HF with advanced CKD (stage 4 and 5) are limited. However, in appropriately selected patients with symptomatic HFpEF, elevated BNP level, HF admission within 1 year, eGFR >30 mL/min per 1.73 m^2, creatinine <2.5 mg/dL, and potassium <5.0 mEq/L, particularly in those with elevated BNP levels, use of spironolactone might be considered with close monitoring of potassium and renal function[58] (Table 6).

Given the universal exclusion of moderate to severe CKD in HF outcomes trials and the lack of reporting on long-term renal outcomes, the true burden of hyperkalemia in the management of chronic CRS is unclear. Collins and coauthors[187] have recently demonstrated in a nationwide electronic medical record (n=1 716 141 with ≥2 potassium values) that the presence of HF increases the fatal risks of hyperkalemia in patients treated with RAAS inhibitors. In this analysis, the overall death rate was 35.7% with hyperkalemia in those subjects with HF, CKD, and DM compared with a death rate of 2.7% in control subjects. In a meta-analysis of clinical trials (n=16 065 subjects), the rates of MRA-associated hyperkalemia (9.5%) were ≈2-fold that of control sub-

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Table 5. Evidence Table of Outcomes in HF in Subjects With CKD Treated With ARBs

Study	n	Study Design	Population	CKD	Concomitant Therapy	Baseline Renal Function	Outcome in CKD Group
Val-HeFT[48]	5010	RCT, valsartan vs placebo	Symptomatic HF, EF <40%	Exclude: Cr >2.5 mg/dL CKD ≥2: 58% Proteinuria without CKD: 52%	β-Blocker 35% Digoxin 67%	GFR 58 mL/min per 1.73 m^2	All-cause mortality: HR, 1.01 (95% CI, 0.85–1.20)
CHARM-Overall[173]	7599	RCT, candesartan vs placebo	Symptomatic HF, EF <40%	Exclude: Cr >3 mg/dL CKD: Cr >2 mg/dL	β-Blocker 55% MRA 17%	NA	Hyperkalemia: Cr >2 vs <2: HR, 4.1 (95% CI, 2.4–7.3) Serious hyperkalemia: Cr >2 vs <2: HR, 3.5 (95% CI, 1.5–7.9)
HEAAL[174]	3846	High- vs low-dose losartan	Symptomatic HF, EF <40%, intolerance of ACE inhibitor	Exclude: Cr >2.5 mg/dL	ACE inhibitor 100% β-Blocker 72% MRA 38%	Cr 1.1 mg/dL	Death and HF admission GFR: <60 mL/min per 1.73 m^2: HR, 0.98 (95% CI, 0.85–1.13) 60–74: HR, 0.94 (95% CI, 0.78–1.14) >75: HR, 0.72 (95% CI, 0.60–0.86)
ELITE[175]	722	Captopril vs losartan	Symptomatic HF, EF <40%	Exclude: Cr >2.5 mg/dL	ACE inhibitor 100% β -Blocker72%	Cr 1.2 mg/dL	Worsening renal function in all groups: 2% (–51% to 36%)

ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CKD, chronic kidney disease; Cr, creatinine; EF, ejection fraction; ELITE, Evaluation of Losartan in the Elderly; GFR, glomerular filtration rate; HEAAL, Heart failure Endpoint Evaluation of Angiotensin II Antagonist Losartan; HF, heart failure; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; NA, not applicable; RCT, randomized controlled trial; and Val-HeFT, Valsartan in Heart Failure.

jects, and among hyperkalemic subjects, 54% were truly caused by the MRA agent.[188] Incorporating the novel oral antihyperkalemic agents (patiromer acetate, sodium zirconium cyclosilicate) into the therapeutic armamentarium of chronic CRS may maximize the additive benefits of MRAs to ACE inhibitors/ARBs.[189]

β-Adrenergic Blockers

β-Adrenergic blockers have been evaluated in numerous RCTs and shown to improve NYHA class and LVEF, to alleviate symptoms, to reduce hospitalization burden, and to prolong survival. β-Blockers that have been shown to reduce mortality in HF include metoprolol and bisoprolol (β-1 receptor blockers), and carvedilol (α-1, β-1, and β-2 receptor blockers) and are recommended as Class 1A evidence for HFrEF by the 2013 American College of Cardiology Foundation/AHA guidelines on the management of HF.[190] Given the paucity of data on β-blockers specific to patients with CKD, the risk/benefit profiles of these drugs in CKD depend on post hoc analyses of major RCTs and observational data.

The MERIT-HF study (Metoprolol CR/XL Controlled Randomized Intervention Trial in Chronic HF) randomized 3991 patients with NYHA class II to IV HF and EF <40% to metoprolol versus placebo. A secondary analysis that looked at the effects of metoprolol across eGFR ranges of >60, 45 to 60, and <45 mL/min per 1.73 m^2 showed significant benefits across all subgroups.[191] The benefits were more pronounced in the group with eGFR <45 mL/min per 1.73 m^2, with a nearly 60% reduction in HHF and mortality. In the SENIORS study (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure), the composite of all-cause mortality and cardiovascular hospital admissions was significantly reduced in 2112 patients >70 years of age with HF who were randomized to nebivolol versus placebo.[192] Although the benefits of nebivolol were observed across tertiles of eGFR, the benefit seen in the lowest eGFR group (<55 mL/min per 1.73 m^2) was not as robust as with MERIT-HF. The CIBIS-II study (Cardiac Insufficiency Bisoprolol Study) randomized 2647 patients with NHYA class III to IV HF with EF <35% to bisoprolol versus placebo.[193] A serum creatinine of >3.4 mg/dL was a prespecified exclusion criterion. The beneficial effects of bisoprolol with significant reductions in all-cause mortality were observed across baseline GFR quartiles. Finally, a meta-analysis of 6 RCTs with β-blockers in patients with CKD and HF showed that β-blockers significantly reduced the risk of all-cause mortality (relative risk reduction [RRR], 28%) and cardiovascular mortality (RRR, 34%) compared with placebo.[194] Tolerability of β-blockers is limited by fluid retention, which may complicate the management of HF, bradycardia, hypotension, and fatigue. MERIT-HF showed similar rates of tolerance across eGFR ranges. However, in the post hoc analyses of CIBIS-II and SENIORS, rates of β-blocker discontinuation were higher in subgroups with eGFR <45 and <55 mL/min per 1.73 m^2, respectively.

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Table 6. Evidence Table of Outcomes in HF in Subjects With CKD Treated With MRAs

Study	n	Study Design	Population	CKD	Concomitant Therapy	Baseline Renal Function	Outcome in CKD Group
RALES[184]	1663	RCT, spironolactone vs placebo	HF, EF <35%	Exclude: Cr >2.5 mg/dL CKD: GFR <60 mL/min per 1.73 m^2 (48%)	ACE inhibitor 94% Digoxin 78%	Cr 1.2 mg/dL	All-cause mortality: HR, 0.68 (95% CI, 0.56–0.84) Worsening renal function: spironolactone vs placebo 17% vs 7%
EMPHASIS-HF[185]	2737	Eplerenone vs placebo	HF, EF<35%	Exclude: GFR <30 mL/min per 1.73 m^2 CKD: CKD >3a: 33%	ACE inhibitor 93% β-blocker 87%	GFR 71 mL/min per 1.73 m^2	HR, 0.66 (95% CI, 0.56–0.78) No difference between subgroups with and without CKD
ARTS-HF[186]	1066	RCT, finerenone with dosage uptitrated vs eplerenone	HFrEF with EF <40%, DM with CKD (GFR >30 cc/min per 1.73 m^2), CKD without DM (GFR 30-60 cc/min per 1.73 m^2)	Exclude: GFR <30 mL/min per 1.73 m^2 CKD: CKD >3a: 71%	NA	GFR 53 mL/min per 1.73 m^2	Decrease in BNP >30%: same in both groups Any adverse event: finerenone less than eplerenone (76.9%) except finerenone 15–20 mg (78.5%) Death, cardiovascular hospitalization, worsening CHF: finerinone better than eplerenone except finerenone 2.5–5mg Hyperkalemia: finerinone better than eplerenone except finerenone 15–20 mg

ACE indicates angiotensin-converting enzyme inhibitor; ARTS-HF, Mineralocorticoid Receptor Antagonist Tolerability Study–Heart Failure; BNP, B-type natriuretic peptide; CHF, congestive heart failure; CKD, chronic kidney disease; Cr, creatinine; DM, diabetes mellitus; EF, ejection fraction; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; GFR, glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; NA, not applicable; RALES, Randomized Aldactone Evaluation Study; and RCT, randomized controlled trial.

In summary, there are varying levels of evidence for goal-directed therapies for HF in the CKD population, with a relative paucity of data in patients with advanced CKD.[195] Figure 4 provides a summary of the relative strengths of evidence in the use of goal-directed medical therapies for HF across the spectrum of GFR ranges for nondialytic CKD.

CARDIORENAL OUTCOMES IN TYPE 2 DIABETES MELLITUS

Cardiovascular disease is a major cause of mortality in patients with type 2 diabetes mellitus (T2DM).[196] Metformin is highly effective, has a very low risk of hypoglycemia, does not cause weight gain, and may reduce cardiovascular events and mortality. Therefore, it is generally recommended as first-line medical therapy for most patients with T2DM when added to lifestyle modification.[197–199] However, many patients do not achieve adequate control with metformin alone, and second and even third medications are often necessary,[198,199] Given the impact of glycemic control on cardiovascular outcomes and the increased cardiovascular risk that was associated with certain glucose-lowering medications, the US Food and Drug Administration outlined the need for cardiovascular safety studies for new glucose-lowering therapies in 2008.[200,201] Subsequently, several trials have reported cardiovascular safety data across multiple classes of glucose-lowering drugs, including GLP-1 (glucagon like peptide-1) receptor agonists, DPP-4 (dipeptidyl peptidase-4) inhibitors, and SGLT-2 (sodium-glucose cotransporter 2) inhibitors, and other trials are ongoing at the time this statement was written. In this section, we highlight key aspects of recently reported safety and cardiovascular outcomes data of the major novel classes of antidiabetic therapy.

SGLT-2 Inhibitors

SGLT-2 inhibitors are one of the latest classes of glucose-lowering therapies available. One SGLT-2 inhibitor, empagliflozin, demonstrated impressive results in the multicenter randomized cardiovascular safety trial EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus).[202] The EMPA-REG OUTCOME Trial randomized 7020 patients with T2DM at high risk for cardiovascular events to receive empagliflozin versus placebo. The trial showed a 14% RRR for the primary composite 3-point major adverse cardiovascular event outcome of cardiovascular death, nonfatal MI, and nonfatal

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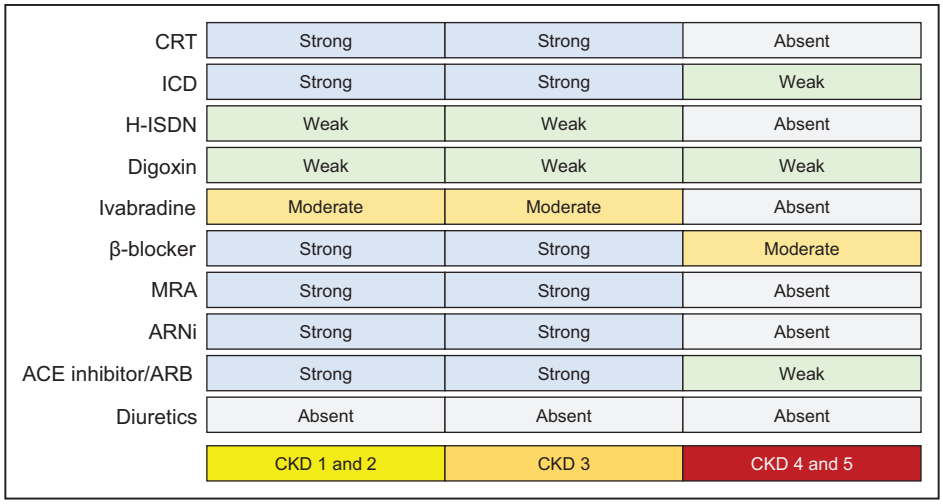

Figure 4. Relative levels of strength of evidence for goal-directed medical therapies in heart failure with reduced ejection fraction across varying stages of nondialytic chronic kidney disease (CKD).
ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; CRT, cardiac resynchronization therapy; H, hydralazine; ICD, implantable cardioverter-defibrillator; ISDN, isosorbide dinitrate; and MRA, mineralocorticoid receptor antagonist.

stroke in patients who received empagliflozin compared with placebo (HR, 0.86 [95% CI, 0.74–0.99]; *P*<0.001 for noninferiority). The major adverse cardiovascular event risk reduction was driven primarily by a 38% RRR in cardiovascular death (HR, 0.62 [95% CI, 0.49–0.77]; *P*<0.001 for noninferiority, *P*<0.04 for superiority). In addition, the trial showed a 35% RRR for HF-related hospitalizations (HR, 0.65 [95% CI, 0.50–0.85]) with a greater impact in preventing first HHF and a lesser impact on prevalent HF. Although renal end points were not the primary outcome in the trial, several prespecified renal outcomes were analyzed, including incident or worsening nephropathy (progression to macroalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy, or death resulting from renal disease) and incident albuminuria (urine albumin to creatinine ratio >30 mg/g). In a post hoc analysis of renal composite outcomes, empagliflozin was associated with a 39% RRR of incident or worsening nephropathy versus placebo (HR, 0.61 [95% CI, 0.55–0.69]).[203] Using adjusted mean differences in eGFR between groups after cessation of the study drug and factoring in the expected GFR decline in patients with T2DM of ≈4 mL/min per 1.73 m^2, the reduction in CKD progression could be translated into delaying the need for dialysis by ≈1 year.[204] Finally, although designed as a safety trial, the cardiovascular outcomes reported tested for both noninferiority and superiority.

The CANVAS program (Canagliflozin Cardiovascular Assessment Study), comprising 2 sister trials, was designed to assess the cardiovascular safety and efficacy of canagliflozin and to evaluate the balance between any potential benefits of the drug and the risks associated with it such as genitourinary infection, diabetic ketoacidosis, limb amputation, and fracture.[205] The CANVAS program integrated data from 2 trials involving a total of 10 142 participants with T2DM and high cardiovascular risk who were randomly assigned to receive canagliflozin or placebo. In the total cohort, the primary end point (composite of cardiovascular death, nonfatal MI, or nonfatal stroke) was reduced with canagliflozin compared with placebo (26.9 versus 31.5 per 1000 patient-years; HR, 0.86 [95% CI, 0.75–0.97]; *P*<0.001 for noninferiority, *P*=0.02 for superiority). A possible benefit of canagliflozin with respect to the progression of albuminuria (HR, 0.73 [95% CI, 0.67–0.79]) and the composite outcome of a sustained 40% reduction in the eGFR, the need for renal replacement therapy, or death resulting from renal causes was also shown (HR, 0.60 [95% CI, 0.47–0.77]). An increased risk of amputation, primarily at the level of the toe or metatarsal, was reported with the use of canagliflozin (6.3 versus 3.4 participants per 1000 patient-years; HR, 1.97 [95% CI, 1.41–2.75]), provoking a US Food and Drug Administration drug safety communication to this effect.[205,206] Risks for amputation were greater in those with baseline peripheral artery disease and even greater in those with prior amputations before enrolling in the trial. On this continuum, a post hoc analysis of EMPA-REG OUTCOME did not show a difference in the incidence of lower limb amputations between treatment groups, but it was limited by manual identification of these adverse events retrospectively.[206] Finally, Verma et al[207] reported no increase in lower limb amputation incidence between groups in a subanalysis of patients with T2DM with peripheral artery disease from EMPA-REG OUTCOME. Because limb revascularization can spare patients with peripheral artery disease the amputation procedure, the regional availability of peripheral

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artery intervention/surgery may have accounted for the variability in reported rates of amputation across trial programs. Currently, it is unknown whether the amputation risk is specific to canagliflozin or extends to other drugs in this class; however, given the biologically plausible off-target effects of SGLT-2 inhibitors, including impairment of the sodium-hydrogen exchanger, which manages cellular pH in ischemia/reperfusion, it is reasonable to avoid this drug class in patients at risk for lower limb ischemia.[208]

The CVD-REAL study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) was an internationally conducted observational study that compared risk of HHF and all-cause mortality in 309 056 patients newly initiated on either SGLT-2 inhibitors or other glucose-lowering drugs after propensity matching.[209] Canagliflozin, dapagliflozin, and empagliflozin accounted for 53%, 42%, and 5% of the total exposure time in the SGLT-2 inhibitor class, respectively. Use of SGLT-2 inhibitors versus other glucose-lowering drugs was associated with lower rates of HHF (HR, 0.61 [95% CI, 0.51–0.70]), death (HR, 0.49 [95% CI, 0.41–0.57]), and HHF or death (HR, 0.54 [95% CI, 0.48–0.60]). These data suggest that the benefits seen with empagliflozin in a randomized trial may be a class effect applicable to a broad population of patients with T2DM. Ongoing trials, including DECLARE-TIMI 58 (Effect of Dapagliflozin on the Incidence of Cardiovascular Events–Thrombolysis in Myocardial Infarction 58), REFORM (Safety and Effectiveness of SGLT-2i in Patients With Heart Failure and Diabetes), VERTIS (Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease), and CREDENCE (Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation), will help shed light on the class and individual drug effects of SGLT-2 inhibitors on cardio-reno-metabolic outcomes

Incretin-Based Therapies

GLP-1 Agonists

GLP-1, an insulin-tropic hormone secreted in the gut after food intake, is the parent compound mediating the effect of 2 classes of glucose-lowering medications: GLP-1 receptor agonists and DPP-4 inhibitors.[210] In the double-blind LEADER trial (Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes), 9340 patients with T2DM and high cardiovascular risk were randomized to liraglutide versus placebo in a noninferiority design.[211] The primary composite outcome in the time-to-event analysis of the first occurrence of death resulting from cardiovascular causes, nonfatal MI, or nonfatal stroke occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients, 13.0%) than in the placebo group (694 of 4672, 14.9%; HR, 0.87 [95% CI, 0.78–0.97]; $P<0.001$ for noninferiority, $P=0.01$ for superiority). SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) showed that semaglutide significantly reduced the primary composite end point of cardiovascular death, nonfatal MI, or nonfatal stroke (HR, 0.74 [95% CI, 0.58–0.95]; $P<0.001$ for noninferiority).[212] These beneficial effects were driven mostly by a significant (39%) reduction in the rate of nonfatal stroke and a nonsignificant (26%) decrease in nonfatal MI, with no significant difference in the rate of cardiovascular death. Moreover, treatment with semaglutide increased retinopathy complications (HR, 1.76 [95% CI, 1.11–2.78]; $P=0.02$). Mann et al[211] reported a significant reduction with liraglutide in the prespecified secondary renal outcome of the composite of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, ESKD, or death caused by renal disease in the LEADER trial (HR, 0.78 [95% CI, 0.67–0.92]). This outcome was driven largely by a reduction in new onset of persistent macroalbuminuria.

The EXSCEL trial (Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes) randomized 14 752 patients with T2DM with or without prior cardiovascular disease to weekly exenatide or placebo with a median follow-up of 3.2 years.[213] A primary composite outcome event occurred in 839 of 7356 patients (11.4%; 3.7 events per 100 person-years) in the exenatide group and in 905 of 7396 patients (12.2%; 4.0 events per 100 person-years) in the placebo group (HR, 0.91 [95% CI, 0.83–1.00]), with the intention-to-treat analysis indicating that exenatide, administered once weekly, was noninferior to placebo with respect to safety ($P<0.001$ for noninferiority) but was not superior to placebo with respect to efficacy ($P=0.06$ for superiority). These results are comparable to results for lixisenatide in the ELIXA trial (Lixisenatide in Patients With Type 2 Diabetes and Acute Coronary Syndrome).[214] Ongoing studies on dulaglutide testing for cardiovascular safety will present results in the future (NCT 13944952).

DPP-4 Inhibitors

The first cardiovascular outcome trials on DPP-4 inhibitors reported neutral effects on the composite of major adverse cardiovascular event outcomes. These include SAVOR-TIMI 53 (Saxagliptin and Cardiovascular Outcomes in Patients With type 2 Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53),[215] EXAMINE (Alogliptin After Acute Coronary Syndrome in Patients With Type 2 Diabetes Trial),[216] and TECOS (Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes).[217] An analysis of the prespecified secondary end point of HHF in the SAVOR-TIMI 53 trial showed a higher risk of HHF in patients treated with saxagliptin versus placebo (HR, 1.27 [95% CI, 1.07–1.51]).[218] This increase in risk was highest among patients with elevated levels

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of natriuretic peptides, previous HF, or CKD. In a post hoc analysis of the end points of cardiovascular death and HHF in the EXAMINE trial, alogliptin had no effect on composite events of cardiovascular death and hospital admission for HF (HR, 1.00 [95% CI, 0.82–1.21]).[219] A prespecified analysis of HHF, HHF or cardiovascular death, and HHF or all-cause death composite outcomes in the TECOS trial showed no significant differences in these outcomes between sitagliptin and placebo.[220] Potential explanations for the inconsistent effects of HHF across these 3 major cardiovascular outcome studies include differing baseline characteristics of severity of disease, hemoglobin A_{1c}, sample size, and degree of CKD (moderate to severe). Additional possibilities include effects of hypoglycemia and altered degradation of substance P and neuropeptide Y, ultimately resulting in sympathetic-mediated vasoconstriction.[221] The CARMELINA trial (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus; NCT01897532) and CAROLINA trial (Cardiovascular Outcome Trial of Linagliptin Versus Glimepiride in Type 2 Diabetes; NCT01243424) will provide new data on the DPP-4 inhibitor linagliptin.

Finally, the emerging pandemic of obesity is a central factor contributing to the maladaptive elements of insulin resistance, hypertension, dyslipidemia, and chronic inflammation central to the cardio-renal-metabolic syndrome. Both obesity and insulin resistance are major risk factors for HFpEF, with impaired insulin metabolic signaling, increased inflammation, and reduced availability of nitric oxide contributing to impaired diastolic mechanics.[222] Similarly, a strong correlation exists between obesity and proteinuria or impaired kidney function, especially with insulin resistance.[223] Population-based strategies targeting obesity are critical in the efforts to reduce the prevalence of cardio-renal-metabolic syndrome, which represents a major burden with regard to morbidity, mortality, and healthcare costs worldwide.

CARDIAC DEVICE THERAPY

Implantable Cardioverter-Defibrillators in CKD

Given the high prevalence of CKD in patients with HF and vice versa, implantable device therapy is part of the therapeutic armamentarium in this population. Although the benefits of placement of implantable cardioverter-defibrillators (ICDs) in patients with HF meeting select criteria are well established in the general population,[224] conflicting data exist on the benefits in patients with HF and CKD. Reduced survival has been consistently described with primary prevention ICDs in CKD, as well as higher complication rates, which include higher infection rates and greater bleeding, central venous stenosis, and tricuspid regurgitation.[225–227] Patients with CKD may have higher defibrillation thresholds than the general population.[228] Pun et al[229] reported outcomes with ICDs for primary prevention in CKD in a meta-analysis of 3 primary prevention ICD RCTs that had data available on renal function: MADIT (Multicenter Automatic Defibrillator Implantation Trial) I, MADIT-II, and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial). ICDs were associated with survival benefit in patients with GFR >60 mL/min per 1.73 m^2 (adjusted HR, 0.49 [95% posterior credible interval, 0.24–0.95]). This was not the case for patients with GFR <60 mL/min per 1.73 m^2 (adjusted HR, 0.80 [95% posterior credible interval, 0.40–1.53]), in whom eGFR did not modify the association between ICDs and rehospitalizations. These findings corroborate data from a propensity-matched analysis to determine the survival benefits with primary prevention ICDs in nondialytic CKD from the Cleveland Clinic CKD Registry.[230] In this analysis, the presence of an ICD was associated with a lower risk of death among those with eGFRs of 45–59 mL/min per 1.73 m^2 (HR, 0.58 [95% CI, 0.44–0.77]) and 30 to 44 mL/min per 1.73 m^2 (HR, 0.65 [95% CI, 0.50–0.85]) but not among those with eGFRs <30 mL/min per 1.73 m^2 (HR, 0.98 [95% CI, 0.71–1.35]). Recently, the DANISH trial (Danish Study to Assess the Efficacy of ICDs in Patients With Non-Ischemic Systolic HF on Mortality) showed that prophylactic ICD implantation in patients with HFrEF not caused by coronary artery disease had no impact on mortality resulting from any cause, including in patients with CKD.[231] However, a meta-analysis by Chen et al[232] specifically included data from RCTs on patients with ESKD and HF who received an ICD and showed that overall survival and 2-year survival were improved in patients with ICD placement. Given that patients with advanced CKD are routinely excluded from major cardiovascular therapy trials and the lack of robust data on survival benefits, decisions to place ICDs for primary prevention in advanced CKD and ESKD must consider patient comorbidities, frailty, and quality of life to balance the risk-benefit profiles with these devices.

Subcutaneous ICDs in CKD

Given the increased complication rates with ICDs that are highly pertinent to the CKD population, subcutaneous ICDs (S-ICDs) have emerged as a potential attractive alternative and offer similar efficacy in pilot data.[233] Two separate single-center experiences reported the safety of the use of S-ICDs in ESKD, and no device-related infections or excessive inappropriate shocks were reported.[234,235] The global EFFORTLESS S-ICD registry (Evaluation of Factors Impacting Clinical Outcomes and Cost Effectiveness of the S-ICD) reported predefined end points of 30-day and 360-day complications and shocks for atrial fibrillation and supraventricular tachycardia.[236] Midterm performance rates on complications, inap-

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propriate shocks, and conversion efficacy were comparable to rates observed with transvenous ICDs. In that registry, 8.6% of patients in the S-ICD arm had CKD at baseline. The presence of CKD was an independent predictor of therapy for polymorphic ventricular tachycardia or ventricular fibrillation (HR for any appropriate therapy with CKD, 2.10 [95% CI, 1.72–4.10]; *P*=0.012; HR for appropriate therapy for polymorphic ventricular tachycardia/ventricular fibrillation with CKD, 2.35 [95% CI, 1.19–4.64]; *P*=0.014). These findings are significant in terms of the greater proportion of patients with CKD included in this trial compared with prior studies and the proof of safety and efficacy at midterm time points. Long-term follow-up data anticipated from this cohort will help define the role of S-ICD in the CKD population.

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) uses a biventricular pacemaker that electrically activates the RV and LV in a synchronized manner, which improves ventricular contraction and reduces the degree of mitral regurgitation. A meta-analysis of 14 RCTs with patients with moderate to severe LV systolic dysfunction with widened QRS demonstrated that CRT significantly improved LVE and quality of life, in addition to reducing all-cause mortality by 22%.[237] Most RCTs have reported few data on patients with CKD with HF. However observational data and post hoc analyses have shed some light on outcomes with CRT in CKD. The MIRACLE study (Multicenter InSync Randomized Clinical Evaluation) evaluated CRT in HF in patients with NHYA class III to IV disease and EF <35%. This trial excluded patients with a serum creatinine >3 mg/dL, but a post hoc analysis found improvements in NYHA class and EF and a reduction in mitral regurgitation across groups with eGFR >90, 60 to 89, and 30 to 59 mL/min per 1.73 m^2.[238,239] In the baseline eGFR category of 30 to 59 mL/min per 1.73 m^2, an improvement in eGFR was noted that was statistically significant. This phenomenon has also been reported in several other studies,[240–243] likely signifying the beneficial effects of improved perfusion and reduced venous congestion. However, despite these benefits, the presence of baseline CKD per se has a negative impact on post-CRT outcomes, as described in a meta-analysis by Bazoukis et al.[244] In this meta-analysis, 13 of 16 studies showed a statistically significant higher risk of all-cause mortality in patients with baseline CKD who underwent CRT. In addition, patients with baseline eGFR <60 mL/min per 1.73 m^2 had an increased risk of death resulting from all causes (HR, 1.66 [95% CI, 1.37–2.02]) compared with patients with eGFR >60 mL/min per 1.73 m^2. Although these data are important when making decisions about the risk-benefit profiles of CRT in patients with CKD, the benefits for reduced hospitalizations and improved quality of life with CRT compared with ICD in CKD should also be factored into the decision algorithm. This is ultimately achieved with a multidisciplinary cardionephrology collaborative approach to achieve improved outcomes with arrhythmia burden reduction and improvement in quality of life while minimizing device-related complications (Table 7).

Table 7. Clinical Considerations in Patients With Advanced CKD Before Placement of Implantable Cardiac Devices

Is there a clear survival benefit in the given patient with device placement? If so, has this been considered by a cardiorenal multidisciplinary team, and has the risk-benefit profile been discussed clearly with the patient?
Has pharmacotherapy for HF been optimized to the extent feasible before device therapy was considered?
If the patient has advanced CKD, have vascular access needs been factored into the decision to implant a cardiac device?
Can subcutaneous or epicardial devices be considered?
How can the dialysis prescription be tailored to reduce rapid flux of electrolytes and fluid shifts?
What strategies can be adopted to reduce the risk of bacteremias with a device in place?
Does the decision to place a cardiac device for either symptom control or potential survival benefits integrate into the overall goals and plan of care for the individual patient?

CKD indicates chronic kidney disease; and HF, heart failure.

Mechanical Circulatory Support and Kidney Function

The use of mechanical circulatory support devices is increasing exponentially in the acute setting of cardiogenic shock and circulatory support during high-risk coronary interventions, for destination therapy in patients with advanced HF, or as a bridge to cardiac transplantation or recovery.[245,246] A full description of the renal impact of short-term and maintenance mechanical circulatory support devices is beyond the scope of this scientific statement; the literature provides a summary.[246–248] At this time, randomized controlled data on head-to-head comparisons between various short-term mechanical circulatory support devices on renal function are lacking. However, in a single-center experience, Flaherty et al[249] demonstrated a reduction in AKI rates with Impella 2.5 (percutaneous ventricular assist device) support during high-risk percutaneous coronary interventions. The effects of continuous versus pulsatile LV assist devices on renal morphology and physiology have been described in animal models.[250] Reduced pulsatile circulation may activate local RAAS, which may have proinflammatory effects and may potentially result in increased vascular stiffness. Smooth muscle hypertrophy of the renal cortical arteries, interstitial nephritis, and periarteritis have also been shown to develop in animal models of continuous perfusion.[251] Welp et al[252] demonstrated lower levels of renin and angiotensin in subjects with pulsatile- versus continuous-flow LV assist

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devices; however, the long-term clinical implications of this observation are unclear. Finally, several clinical factors affect long-term kidney function in patients with maintenance mechanical circulatory support, including preexisting CKD, device-related malfunction or subclinical hemolysis, progressive RV failure with prolonged LV assist device support, and the chronic maladaptive neurohumoral changes seen in patients with these devices.

HF AND KIDNEY TRANSPLANT

KT is the treatment of choice for patients with ESKD, resulting in improved quantity and quality of life at lower cost to the healthcare system than long-term dialysis.[253,254] HF is a major cause of morbidity and mortality in patients with ESKD, with a reported prevalence among patients on dialysis of 12 to 36 times that of the general population.[255–257] In a historic cohort study of >1900 patients enrolled in the US Renal Data System Dialysis Morbidity and Mortality Study Wave 2, the incidence of HF was 71 per 1000 person-years, and associated 3-year mortality after HHF was 83%.[258] de Mattos et al[259] demonstrated a strong correlation between reduced EF and mortality in a population selected for KT wait listing such that every 1-point increase in LVEF was associated with a 2.5% decrease in adjusted mortality risk. The ongoing burden of HF after KT is illustrated by the increasing contribution of HF to cardiovascular disease–related hospitalizations after KT since 2005, with HF accounting for 16% of all hospitalizations.[260]

Impact of KT on HFrEF

An improvement in LVEF after KT in patients with HF before transplantation has been described in several single-center experiences.[261–263] Wali et al[264] described a cohort of 103 patients with LVEF <40% (mean EF, 31.6±6.7%) with a median of 2 HHFs before KT evaluation. Of this cohort, 51% had documented coronary artery disease but none had inducible ischemia at the time of transplantation. Patients were further stratified by post-KT EF into 3 groups: group 1, EF >50%; group 2, EF of 40% to 50%; and group 3, EF <40%. Although post-KT mortality rose with lower baseline EF (group 1, 8%; group 2, 62%; group 3, 62%; $P<0.001$), most patients experienced an improvement in EF with KT. Specifically, by 1 year after KT, 72 of 103 patients (70%) had an EF >50%, and 16 patients improved their EF to 40% to 50%. Overall, 86% of patients had an EF improvement of at least 5% by multigated acquisition scanning. Longer pre-KT dialysis duration was the only factor that independently predicted failure to improve LVEF. Reversal of uremic cardiomyopathy after KT has also been described in case reports, including clinically important improvements in EF, LV end-diastolic dimensions, and the degree of mitral regurgitation.[265]

De Novo/Preexisting LV Dysfunction and Renal Allograft Outcomes

Lentine et al[266] described the risk, predictors, and outcomes associated with de novo HF after KT among Medicare-insured KT candidates and recipients captured in the US Renal Data System. Among 27 011 KT recipients (1995–2011), the cumulative incidence of de novo HF was 10.2% at 12 months and 18.3% at 36 months and decreased to less than the demographic-adjusted incidence on the waiting list beyond the early posttransplantation period. De novo HF predicted death (HR, 2.6 [95% CI, 2.4–2.9]) and death-censored graft failure (HR, 2.7 [95% CI, 2.4–3.0]) in this cohort. A report of a 2-center retrospective Canadian study of 638 KT recipients who were free of cardiac disease 1 year after transplantation described the risk factors, incidence, and relationships between de novo HF and ischemic heart disease after KT (median follow-up, 7 years).[267] De novo HF occurred as frequently as de novo ischemic heart disease (1.26 versus 1.22 events per 100 patient-years, respectively) and appeared to carry a similar prognosis (mortality: RR, 1.78 [95% CI, 1.21–2.61] for HF versus RR,1.50 [95% CI, 1.05–2.13] for ischemic heart disease). The incidence of HF was considerably higher than in the Framingham cohort, whereas the incidence of ischemic heart disease was not, raising the possibility that KT might correspond more to a state of accelerated HF than to accelerated atherosclerosis. In a single-center experience of 653 KT recipients, 18% had an EF <45% based on single-photon emission computed tomography imaging before transplantation. Over an average of 3 years of follow-up, LV dysfunction was an independent predictor of cardiac death (HR, 4.8 [95% CI, 2.09–11.21]), overall mortality (HR, 2.0; $P=0.01$), and cardiac hospitalizations.[268] Another study compared 19 KT recipients with preexisting EF <50% with paired control subjects who received a kidney from the same donor but did not have reduced EF.[269] Patients with reduced EF experienced higher rates of delayed graft function, as well as longer renal recovery time, before becoming dialysis free (19.8 days versus 12 days; $P=0.01$). These data underscore the impact of both preexisting and new-onset LV dysfunction on allograft and patient outcomes after KT.

Management of HF in KT

There are limited controlled data on the optimal pharmacotherapy of HF specific to KT recipients. Management of HF in the context of KT involves integrating available evidence-based therapies for HF in CKD (based on the degree of allograft function), transplantation-specific factors such as immunosuppressive agent choice, and factors influencing patient and allograft outcomes such as rejection episodes and the development of new-onset diabetes mellitus after transplantation.

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There is conflicting evidence on the efficacy of RAAS inhibition and HF outcomes in KT recipients. Paoletti et al[270] randomized 70 KT recipients on standard immunosuppression with calcineurin inhibitors (cyclosporine or tacrolimus), mycophenolate mofetil, and steroids to lisinopril versus usual care. Event-free survival for a composite end point of death, major cardiovascular events, renal graft loss, or creatinine doubling was analyzed according to a modified intention-to-treat analysis. Compared with control subjects, the ACE inhibitor group had significantly better survival free of the combined end point (P=0.01) and free of major cardiovascular events (P=0.003), but no significant differences in renal outcomes were noted. In Cox regression analysis, ACE inhibitor therapy was the strongest predictor of survival free of major cardiovascular events (HR, 0.21 [95% CI, 0.07–0.64]). In contrast, SECRET (Study on Evaluation of Candesartan Cilexetil After Kidney Transplantation), which randomized 700 KT recipients to candesartan versus placebo, was terminated prematurely after a mean follow-up of 20 months because of a much lower than expected rate of the primary outcome of all-cause mortality, cardiovascular morbidity, or graft failure. Knoll et al[271] randomized 213 KT recipients to ramipril versus placebo in an intention-to-treat trial with a primary outcome of all cause death, ESKD, or doubling of serum creatinine. The primary outcome occurred in 17% of patients (19 of 109) in the placebo group and 14% (14 of 103) in the ramipril group (HR, 0.76 [95% CI, 0.38–1.51]). At 48 months, the primary outcome occurred in 25% of the placebo group and 24% of the ramipril group (HR, 0.96 [95% CI, 0.55–1.65]; absolute risk difference, –0.5% [95% CI, –12.0 to 11.1]). Fourteen percent of patients in the ramipril group and 10% in the placebo group died over the follow-up, but this difference in mortality was not statistically significant (HR, 1.45 [95% CI, 0.66–3.21]). Adverse events were more common in the ramipril group than in the placebo group (38% versus 22%; P=0·02). In a meta-analysis of 8 trials examining clinical outcomes with RAAS inhibition in KT recipients by Hiremath et al,[158] only 1 trial specifically used HF as a primary outcome. No difference in all-cause mortality was observed with ACE inhibitor/ARB therapy versus placebo (RR for all-cause death, 0.96 [95% CI, 0.62–1.51]; P=0.9). A significantly higher risk for hyperkalemia with RAAS blockade was noted (RR, 2.44 [95% CI, 1.53–3.90]). Currently, there is a paucity of data on the impact of pretransplantation dialysis modality, β-blockers, vasodilators, and MRAs on HF outcomes after KT, highlighting the need for future studies to optimize outcomes.

Impact of PH on KT Outcomes

PH is highly prevalent in patients with CKD and is associated with worse post-KT outcomes. In a cohort of 215 KT recipients, Issa et al[272] found that compared with RV systolic pressure <50 mm Hg before KT, a PA systolic pressure >50 mm Hg was associated with nearly 4 times the post-KT mortality over a mean follow-up of 22.8 months (HR, 3.75; P=0.025). Zlotnick et al[273] demonstrated an association of PH with early kidney allograft dysfunction after deceased donor transplantation. In a cohort of 638 KT recipients, patients with (versus without) PH before transplantation had lower graft survival rate at 5 years (54.6% versus 76.0%; P<0.05) and were nearly twice as likely to experience all-cause graft failure (crude HR, 1.80 [95% CI, 1.55–2.08]; adjusted HR, 1.3 [95% CI, 1.11–1.51]) during the study period.[274] In a single-center cohort of 35 simultaneous heart-kidney transplant recipients (1996–2015), preoperative RV systolic pressure was higher in those with (versus without) delayed graft function of the renal allograft (45.2±13 mm Hg versus 36.5±10 mm Hg; P=0.03).[275] There was also a significant association between delayed graft function and reduced median GFR at 1 and 3 years after transplantation, underscoring the impact of preoperative PH on short- and long-term renal allograft outcomes in simultaneous heart-kidney transplant recipients. The complexity and multifactorial pathogenesis of PH in potential KT candidates warrants a careful multidisciplinary evaluation to allow detection and optimization of PH before transplantation given the significant impact on post-KT outcomes.[276] A comprehensive approach to management of PH in KT candidates is summarized in Figure 5.

PALLIATIVE CARE IN CRS

The backdrop of high mortality, healthcare resource use, and poor quality of life with advanced CRS suggests that these patients would benefit from concurrent involvement with palliative care.[277] The interlinked cycle of heart and kidney failure clinically manifests with symptoms related to volume overload and an ineffective cardiac pump: dyspnea, fatigue, and chronic pain. In addition to these symptoms being the most common in the HF and CKD populations, depression is another highly prevalent symptom in these diseases, with the symptom burden with HF and advanced CKD being comparable to that in patients with advanced lung and pancreatic cancer.[278]

Bone and mineral disorders associated with CKD are associated with high rates of skeletal fractures with falls. Pain is highly prevalent and multifactorial in this population, and undertreatment results in poor quality of life. The presence of pain should be assessed in all patients with CRS through pain quantification with scales such as PQRST (presence of pain, quality of pain, radiation, precipitating or relieving factors, and timing) and temporal follow-up with tools such as the modified Edmonton Symptom Assessment Scale, which is validated in both

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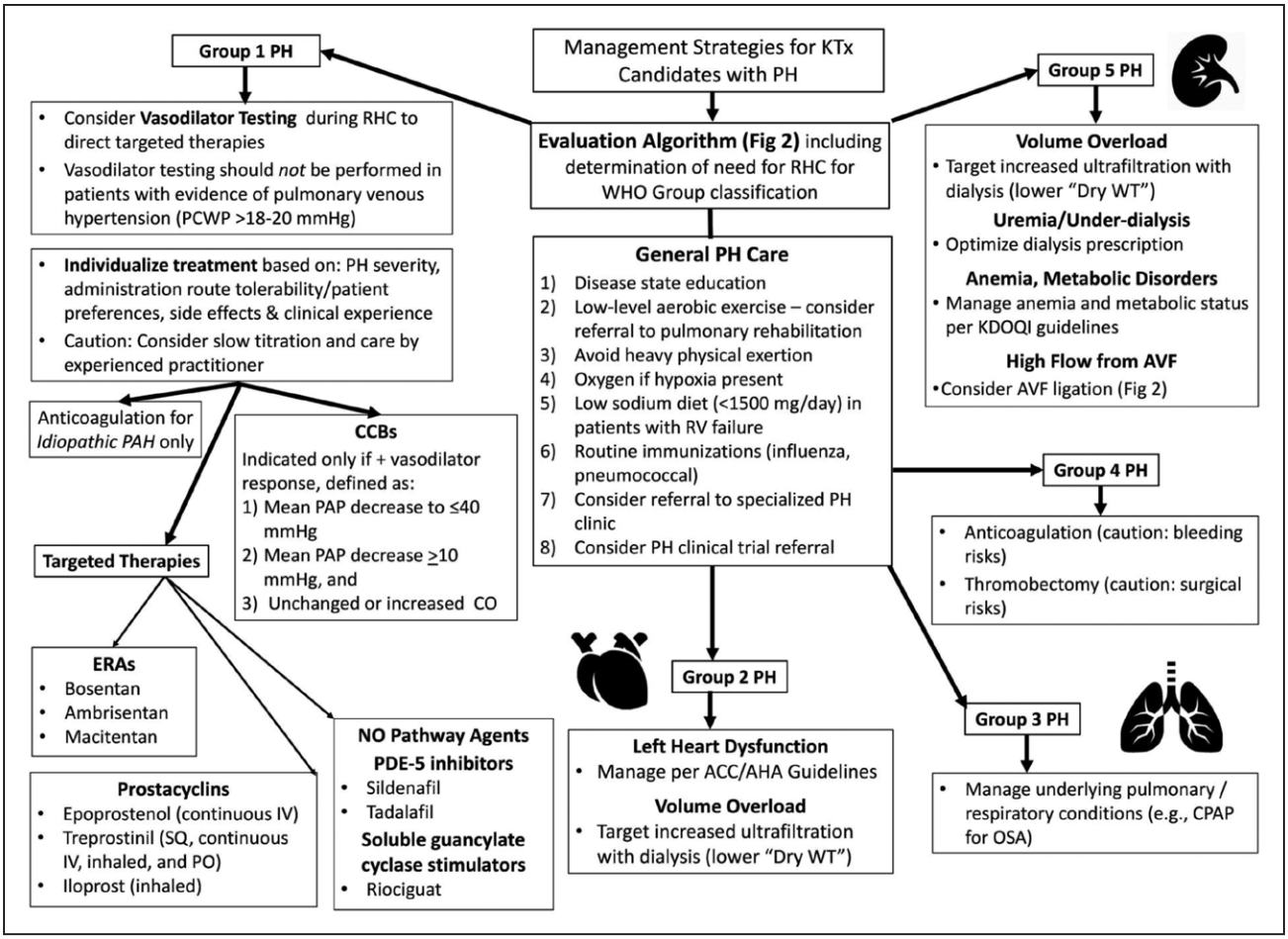
Management Strategies for KTx Candidates with PH
Evaluation Algorithm (Fig 2) including determination of need for RHC for WHO Group classification
Group 1 PH
Consider Vasodilator Testing during RHC to direct targeted therapies
Vasodilator testing should not be performed in patients with evidence of pulmonary venous hypertension (PCWP >18-20 mmHg)
Individualize treatment based on: PH severity, administration route tolerability/patient preferences, side effects & clinical experience
Caution: Consider slow titration and care by experienced practitioner
Anticoagulation for Idiopathic PAH only
Targeted Therapies
CCBs
Indicated only if + vasodilator response, defined as:
1) Mean PAP decrease to ≤40 mmHg
2) Mean PAP decrease ≥10 mmHg, and
3) Unchanged or increased CO
ERAs
Bosentan
Ambrisentan
Macitentan
Prostacyclins
Epoprostenol (continuous IV)
Treprostinil (SQ, continuous IV, inhaled, and PO)
Iloprost (inhaled)
NO Pathway Agents
PDE-5 inhibitors
Sildenafil
Tadalafil
Soluble guancylate cyclase stimulators
Riociguat
General PH Care
1) Disease state education
2) Low-level aerobic exercise – consider referral to pulmonary rehabilitation
3) Avoid heavy physical exertion
4) Oxygen if hypoxia present
5) Low sodium diet (<1500 mg/day) in patients with RV failure
6) Routine immunizations (influenza, pneumococcal)
7) Consider referral to specialized PH clinic
8) Consider PH clinical trial referral
Group 2 PH
Left Heart Dysfunction
Manage per ACC/AHA Guidelines
Volume Overload
Target increased ultrafiltration with dialysis (lower "Dry WT")
Group 5 PH
Volume Overload
Target increased ultrafiltration with dialysis (lower "Dry WT")
Uremia/Under-dialysis
Optimize dialysis prescription
Anemia, Metabolic Disorders
Manage anemia and metabolic status per KDOQI guidelines
High Flow from AVF
Consider AVF ligation (Fig 2)
Group 4 PH
Anticoagulation (caution: bleeding risks)
Thromobectomy (caution: surgical risks)
Group 3 PH
Manage underlying pulmonary / respiratory conditions (e.g., CPAP for OSA)

Figure 5. Concept map outlining the workup of pulmonary hypertension (PH) in patients with chronic kidney disease being considered for potential kidney transplantation (KTx).

ACC/AHA indicates American College of Cardiology/American Heart Association; AVF, arteriovenous fistula; CCB, calcium channel blockers; CO, cardiac output; CPAP, continuous positive airway pressure; ERA, endothelin receptor antagonist; IV, intravenous; KDOQI, Kidney Disease Outcomes Quality Initiative; NO, nitric oxide; OSA, obstructive sleep apnea; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PDE-5, phosphodiesterase inhibitor-5; PO, by mouth; RHC, right-sided heart catheterization; RV, right ventricular; SQ, subcutaneous; WHO, World Health Organization; and WT, weight. The "Fig 2" referenced in the figure is Figure 2 in the original article.[276] Reprinted from Lentine et al[276] with permission. Copyright © 2016, Wolters Kluwer Health, Inc.

CKD and HF.[279] Nonsteroidal anti-inflammatory agents are contraindicated in both HF and CKD with the propensity to cause AKI, salt and water retention, and exacerbations of HF. Opioids are generally underprescribed in this population, and data suggest that agent choice is often inappropriate for CKD.[280] Morphine is mostly contraindicated for chronic pain management with moderate to severe CKD because its metabolite (morphine 6 glucuronide) accumulates in CKD, resulting in confusion, delirium, myoclonus, and respiratory depression. Safer alternative opioids include hydromorphone, oxycodone, and fentanyl.[280] Methadone is safe in HF and CKD for chronic stable pain control and must be used with careful QTc interval monitoring. Dyspnea is multifactorial in this population, and endurance exercise is beneficial in improving quality of life in HF.[281] Peritoneal dialysis has been used in diuretic refractory HF with benefits in symptom control.[282] Opioid therapy should be considered when dyspnea is refractory to maximal HF and volume management and exercise therapy is maximized or inefficient. Depression is highly prevalent in patients with CKD and HF and is an independent predictor of mortality.[283] Two randomized trials of sertraline in non–dialysis-dependent CKD and in HF failed to show benefit over placebo at 12 weeks.[284,285] Appropriate use of palliative healthcare services in outpatients has been shown to reduce emergency department visits and hospital admissions in patients with advanced CKD[286] and is an underused strategy in patients with advanced CRS. Effective communication, advanced care planning, and appropriate use of hospice resources are essential parts of the care of the patient with advanced CRS with the incorporation of these services into the multidisciplinary care approach for this condition.

FUTURE DIRECTIONS IN CARDIORENAL MEDICINE

Over the past decade, several strides have been made across the globe in streamlining the multidisciplinary ap-

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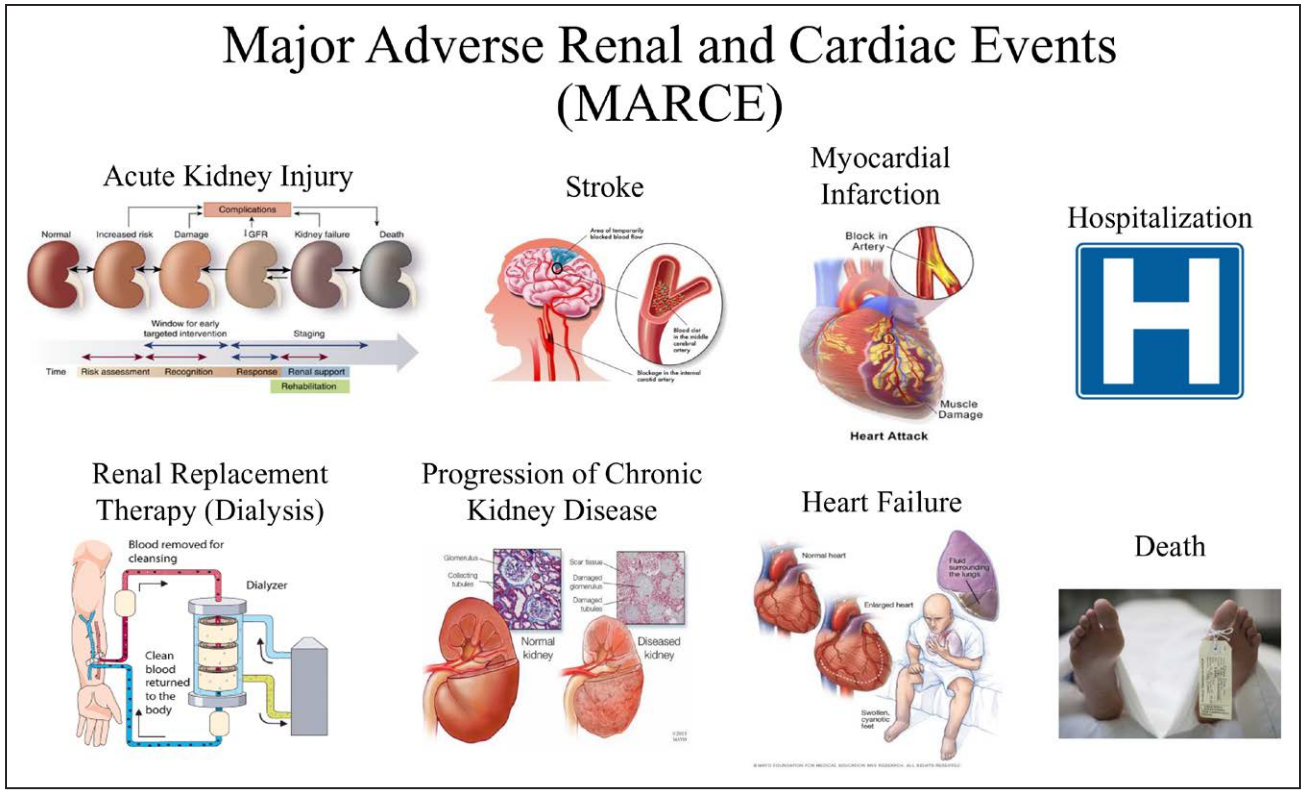

Figure 6. Outline of major adverse renal and cardiovascular events as a novel target clinical end point in cardiorenal trials.
GFR indicates glomerular filtration rate.
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proach to cardiorenal medicine. These have included establishing disease definitions and specific nomenclature, understanding the pathophysiology of the bidirectional cross-talk involved in cardiorenal disease, developing novel biomarkers to detect early injury and to aid prognosis, and introducing novel imaging techniques. The introduction of clinically meaningful composite cardiorenal outcomes such as major adverse renal cardiovascular events (composite of MI, need for renal replacement therapy, stroke, HF, hospitalizations for cardiac reasons, hospitalization for renal reasons, and death)[287] and major adverse kidney events (composite of persistently impaired renal function, new hemodialysis, and death) allows the clinical consequences of AKI and the effects of different interventions to be defined more accurately[288,289] (Figure 6). Initiatives such as the SONG collaborative (Standardized Outcomes in Nephrology) that emphasize core outcome measures reporting across the spectrum of kidney disease in trials based on patient and physician priorities are a valuable addition to future cardiorenal trial outcomes reports.[290] However, patients with the dual burden of heart and kidney disease continue to experience unacceptably high rates of hospitalization, symptom burden, and mortality. Early concerted efforts to identify and prevent decompensated CRS are lacking at the individual and institutional levels, with emphasis still being placed on individual specialty views on this topic. The writing group endorses the need for a dedicated cardiorenal interdisciplinary team that spearheads early identification of patients with decompensated CRS and jointly manages appropriate clinical interventions across the inpatient and outpatient settings (Table 8). This collaborative would also oversee

Table 8. Summary Table of Key Aspects of the Diagnosis and Management of CRS

Distinguishing true AKI from functional causes of fluctuations in serum creatinine in the context of diuresis for acute decompensated HF is critical in ensuring delivery of goal-directed medical therapies.
Identifying the factors contributing to diuretic resistance is a key step in optimizing decongestion in CRS.
Biomarkers of cardiac and kidney injury represent a new dimension in the diagnostic algorithm in evaluating HF with impaired kidney function and offer prognostic value in acute and chronic CRS.
High-quality data for goal-directed medical therapy in chronic CRS with moderate to severe decline in kidney function are lacking. They represent areas of research in future studies.
A multidisciplinary approach is required for cardiac device therapies to reduce arrhythmia burden in patients with HF and CKD.
Palliative care is an underused strategy in patients with the dual burden of HF and advanced CKD.
A cardionephrology multidisciplinary approach is essential in the joint management of patients with CRS with an emphasis on core outcome measures based on patient and physician priorities.

AKI indicates acute kidney injury; CKD, chronic kidney disease; CRS, cardiorenal syndrome; and HF, heart failure.

cross-training among nephrology and cardiology fellows and nursing and allied healthcare providers in both specialties to foster a deeper understanding of the intricacies of cardiorenal cross-talk. There is a critical need for guidelines and best clinical practice models from major cardiology and nephrology professional societies geared specifically toward cardiorenal medicine outcomes and for research funding in both specialties to focus on the needs of future therapies. Implementation of local and national task forces that emphasize quality improvement measures in cardiorenal disease and the introduction of national quality benchmarks for cardiorenal outcomes will help reduce its morbidity, mortality, and economic burden. Finally, implementing cross-specialty educational programs across all levels in cardiology and nephrology will help train future physicians who have the ability to diagnose, treat, and prevent the disease burden associated with CRS in a precise, clinically effective, and cost-favorable manner.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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REFERENCES

1. Bright R. Cases and observations illustrative of renal disease accompanied by the secretion of albuminous urine. *Guys Hospital Reports*. 1836: 338–400.
2. National Heart, Lung, and Blood Institute. NHLBI Working Group: cardiorenal connections in heart failure and cardiovascular disease, 2004. 2004. https://www.nhlbi.nih.gov/events/2004/cardio-renal-connections-heart-failure-and-cardiovascular-disease. Accessed February 15, 2018.
3. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, Bellomo R, Berl T, Bobek I, Cruz DN, Daliento L, Davenport A, Haapio M, Hillege H, House AA, Katz N, Maisel A, Mankad S, Zanco P, Mebazaa A, Palazzuoli A, Ronco F, Shaw A, Sheinfeld G, Soni S, Vescovo G, Zamperetti N, Ponikowski P. Cardio-renal syndromes: report from the Consensus Conference of the Acute Dialysis Quality Initiative. *Eur Heart J*. 2010;31:703–711.
4. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008;52:1527–1539. doi: 10.1016/j.jacc.2008.07.051
5. Hatamizadeh P, Fonarow GC, Budoff MJ, Darabian S, Kovesdy CP, Kalantar-Zadeh K. Cardiorenal syndrome: pathophysiology and potential targets for clinical management. *Nat Rev Nephrol*. 2013;9:99–111. doi: 10.1038/nrneph.2012.279
6. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure: definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8:R204–R212.
7. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:R31. doi: 10.1186/cc5713
8. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int*. 2012;suppl 4:1–138.
9. Ahmad T, Jackson K, Rao VS, Tang WHW, Brisco-Bacik MA, Chen HH, Felker GM, Hernandez AF, O'Connor CM, Sabbisetti VS, Bonventre JV, Wilson FP, Coca SG, Testani JM. Worsening renal function in patients with acute heart failure undergoing aggressive diuresis is not associated with tubular injury. *Circulation*. 2018;137:2016–2028. doi: 10.1161/CIRCULATIONAHA.117.030112.
10. Damman K, Tang WH, Testani JM, McMurray JJ. Terminology and definition of changes renal function in heart failure. *Eur Heart J*. 2014;35:3413–3416. doi: 10.1093/eurheartj/ehu320
11. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med*. 1999;341:577–585. doi: 10.1056/NEJM199908193410806
12. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP; ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J*. 2005;149:209–216. doi: 10.1016/j.ahj.2004.08.005
13. Sweitzer NK, Lopatin M, Yancy CW, Mills RM, Stevenson LW. Comparison of clinical features and outcomes of patients hospitalized with heart failure and normal ejection fraction (> or=55%) versus those with mildly reduced (40% to 55%) and moderately to severely reduced (<40%) fractions. *Am J Cardiol*. 2008;101:1151–1156. doi: 10.1016/j.amjcard.2007.12.014
14. Winton FR. The influence of venous pressure on the isolated mammalian kidney. *J Physiol*. 1931;72:49–61.
15. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WHW. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol*. 2009;53:589–596. doi: 10.1016/j.jacc.2008.05.068
16. Damman K, Navis G, Smilde TD, Voors AA, van der Bij W, van Veldhuisen DJ, Hillege HL. Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. *Eur J Heart Fail*. 2007;9:872–878. doi: 10.1016/j.ejheart.2007.05.010
17. Merrill AJ. Edema and decreased renal blood flow in patients with chronic congestive heart failure; evidence of forward failure as the primary cause of edema. *J Clin Invest*. 1946;25:389–400.
18. Ljungman S, Laragh JH, Cody RJ. Role of the kidney in congestive heart failure: relationship of cardiac index to kidney function. *Drugs*. 1990;39(suppl 4):10–21.
19. Ichikawa I, Pfeffer JM, Pfeffer MA, Hostetter TH, Brenner BM. Role of angiotensin II in the altered renal function of congestive heart failure. *Circ Res*. 1984;55:669–675.
20. Ruggenenti P, Remuzzi G. Worsening kidney function in decompensated heart failure: treat the heart, don't mind the kidney. *Eur Heart J*. 2011;32:2476–2478. doi: 10.1093/eurheartj/ehr242
21. Ljungman S, Kjekshus J, Swedberg K. Renal function in severe congestive heart failure during treatment with enalapril (the Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS] Trial). *Am J Cardiol*. 1992;70:479–487.
22. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, Yancy CW, Califf RM, Stevenson LW, Hill JA. Cardiorenal interactions: insights from the ESCAPE trial. *J Am Coll Cardiol*. 2008;51:1268–1274. doi: 10.1016/j.jacc.2007.08.072
23. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol*. 2009;53:582–588. doi: 10.1016/j.jacc.2008.08.080
24. Mullens W, Abrahams Z, Skouri HN, Francis GS, Taylor DO, Starling RC, Paganini E, Tang WH. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? *J Am Coll Cardiol*. 2008;51:300–306. doi: 10.1016/j.jacc.2007.09.043
25. Kanjanahattakij N, Sirinvaravong N, Aguilar F, Agrawal A, Krishnamoorthy P, Gupta S. High right ventricular stroke work index is associated with worse kidney function in patients with heart failure with preserved ejection fraction. *Cardiorenal Med*. 2018;8:123–129. doi: 10.1159/000486629
26. Barger AC, Yates FE, Rudolph AM. Renal hemodynamics and sodium excretion in dogs with graded valvular damage, and in congestive failure. *Am J Physiol*. 1961;200:601–608. doi: 10.1152/ajplegacy.1961.200.3.601
27. Ledsome JR, Kan WO. Reflex changes in hindlimb and renal vascular resistance in response to distention of the isolated pulmonary arteries of the dog. *Circ Res*. 1977;40:64–72.
28. Schrier RW. Body fluid volume regulation in health and disease: a unifying hypothesis. *Ann Intern Med*. 1990;113:155–159.
29. Adnot S, Chabrier PE, Andrivet P, Viossat I, Piquet J, Brun-Buisson C, Gutkowska Y, Braquet P. Atrial natriuretic peptide concentrations and pulmonary hemodynamics in patients with pulmonary artery hypertension. *Am Rev Respir Dis*. 1987;136:951–956. doi: 10.1164/ajrccm/136.4.951
30. Nagaya N, Nishikimi T, Okano Y, Uematsu M, Satoh T, Kyotani S, Kuribayashi S, Hamada S, Kakishita M, Nakanishi N, Takamiya M, Kunieda T, Matsuo H, Kangawa K. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. *J Am Coll Cardiol*. 1998;31:202–208.
31. Dong SJ, Smith ER, Tyberg JV. Changes in the radius of curvature of the ventricular septum at end diastole during pulmonary arterial and aortic constrictions in the dog. *Circulation*. 1992;86:1280–1290.
32. Gan C, Lankhaar JW, Marcus JT, Westerhof N, Marques KM, Bronzwaer JG, Boonstra A, Postmus PE, Vonk-Noordegraaf A. Impaired left ventricular filling due to right-to-left ventricular interaction in patients with pulmonary arterial hypertension. *Am J Physiol Heart Circ Physiol*. 2006;290:H1528–H1533. doi: 10.1152/ajpheart.01031.2005
33. Driscoll DJ, Offord KP, Feldt RH, Schaff HV, Puga FJ, Danielson GK. Five- to fifteen-year follow-up after Fontan operation. *Circulation*. 1992;85:469–496.
34. Sawatani S, Mandell G, Kusaba E, Schraut W, Cascade P, Wajszczuk WJ, Kantrowitz A. Ventricular performance following ablation and prosthetic replacement of right ventricular myocardium. *Trans Am Soc Artif Intern Organs*. 1974;20B:629–636.
35. Haase M, Muller C, Damman K, Murray PT, Kellum JA, Ronco C, McCullough PA. Pathogenesis of cardiorenal syndrome type 1 in acute decompensated heart failure: workgroup statements from the Eleventh Consensus Conference of the Acute Dialysis Quality Initiative (ADQI). *Contrib Nephrol*. 2013;182:99–116.
36. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, Gutiérrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St John Sutton M, Ojo A, Gadegbeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro-O M, Kusek JW, Keane MG, Wolf M. FGF23 induces left ventricular hypertrophy. *J Clin Invest*. 2011;121:4393–4408. doi: 10.1172/JCI46122
37. Ganda A, Onat D, Demmer RT, Wan E, Vittorio TJ, Sabbah HN, Colombo PC. Venous congestion and endothelial cell activation in acute

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decompensated heart failure. *Curr Heart Fail Rep*. 2010;7:66–74. doi: 10.1007/s11897-010-0009-5
38. Virzì GM, Zhang J, Nalesso F, Ronco C, McCullough PA. The role of dendritic and endothelial cells in cardiorenal syndrome. *Cardiorenal Med*. 2018;8:92–104. doi: 10.1159/000485937
39. Ismail Y, Kasmikha Z, Green HL, McCullough PA. Cardio-renal syndrome type 1: epidemiology, pathophysiology, and treatment. *Semin Nephrol*. 2012;32:18–25. doi: 10.1016/j.semnephrol.2011.11.003
40. Cheng YJ, Yao FJ, Liu LJ, Tang K, Lin XX, Li WJ, Zhang J, Wu SH. B-type natriuretic peptide and prognosis of end-stage renal disease: a meta-analysis. *PLoS One*. 2013;8:e79302. doi: 10.1371/journal.pone.0079302
41. Husain-Syed F, McCullough PA, Birk HW, Renker M, Brocca A, Seeger W, Ronco C. Cardio-pulmonary-renal interactions: a multidisciplinary approach. *J Am Coll Cardiol*. 2015;65:2433–2448. doi: 10.1016/j.jacc.2015.04.024
42. Shlipak MG, Katz R, Fried LF, Jenny NS, Stehman-Breen C, Newman AB, Siscovick D, Psaty BM, Sarnak MJ. Cystatin-C and mortality in elderly persons with heart failure. *J Am Coll Cardiol*. 2005;45:268–271. doi: 10.1016/j.jacc.2004.09.061
43. Lassus J, Harjola VP, Sund R, Siirilä-Waris K, Melin J, Peuhkurinen K, Pulkki K, Nieminen MS; FINN-AKVA Study Group. Prognostic value of cystatin C in acute heart failure in relation to other markers of renal function and NT-proBNP. *Eur Heart J*. 2007;28:1841–1847. doi: 10.1093/eurheartj/ehl507
44. Arimoto T, Takeishi Y, Niizeki T, Takabatake N, Okuyama H, Fukui A, Tachibana H, Nozaki N, Hirono O, Tsunoda Y, Miyashita T, Shishido T, Takahashi H, Koyama Y, Kubota I. Cystatin C, a novel measure of renal function, is an independent predictor of cardiac events in patients with heart failure. *J Card Fail*. 2005;11:595–601. doi: 10.1016/j.cardfail.2005.06.001
45. Manzano-Fernández S, Boronat-Garcia M, Albaladejo-Otón MD, Pastor P, Garrido IP, Pastor-Pérez FJ, Martínez-Hernández P, Valdés M, Pascual-Figal DA. Complementary prognostic value of cystatin C, N-terminal pro-B-type natriuretic peptide and cardiac troponin T in patients with acute heart failure. *Am J Cardiol*. 2009;103:1753–1759. doi: 10.1016/j.amjcard.2009.02.029
46. Jackson CE, Solomon SD, Gerstein HC, Zetterstrand S, Olofsson B, Michelson EL, Granger CB, Swedberg K, Pfeffer MA, Yusuf S, McMurray JJ; CHARM Investigators and Committees. Albuminuria in chronic heart failure: prevalence and prognostic importance. *Lancet*. 2009;374:543–550. doi: 10.1016/S0140-6736(09)61378-7
47. Masson S, Latini R, Milani V, Moretti L, Rossi MG, Carbonieri E, Frisinghelli A, Minneci C, Valisi M, Maggioni AP, Marchioli R, Tognoni G, Tavazzi L; on behalf of the GISSI-HF Investigators. Prevalence and prognostic value of elevated urinary albumin excretion in patients with chronic heart failure: data from the GISSI-Heart Failure trial. *Circ Heart Fail*. 2010;3:65–72. doi: 10.1161/CIRCHEARTFAILURE.109.881805
48. Anand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN. Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. *Circulation*. 2009;120:1577–1584. doi: 10.1161/CIRCULATIONAHA.109.853648
49. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*. 2003;108:2154–2169. doi: 10.1161/01.CIR.0000095676.90936.80
50. Smilde TD, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. *Circulation*. 2006;114:1572–1580. doi: 10.1161/CIRCULATIONAHA.105.610642
51. Dupont M, Shrestha K, Singh D, Finucan M, Tang WH. Lack of concordance in defining worsening renal function by rise in creatinine vs rise in cystatin C. *Congest Heart Fail*. 2013;19:E17–E21. doi: 10.1111/chf.12015
52. Wang K, Kestenbaum B. Proximal tubular secretory clearance: a neglected partner of kidney function. *Clin J Am Soc Nephrol*. 2018;13:1291–1296. doi: 10.2215/CJN.12001017
53. Perazella MA, Coca SG, Hall IE, Iyanam U, Koraishy M, Parikh CR. Urine microscopy is associated with severity and worsening of acute kidney injury in hospitalized patients. *Clin J Am Soc Nephrol*. 2010;5:402–408. doi: 10.2215/CJN.06960909
54. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A; NGAL Meta-Analysis Investigator Group. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis*. 2009;54:1012–1024. doi: 10.1053/j.ajkd.2009.07.020
55. Mortara A, Bonadies M, Mazzetti S, Fracchioni I, Delfino P, Chioffi M, Bersano C, Specchia G. Neutrophil gelatinase-associated lipocalin predicts worsening of renal function in acute heart failure: methodological and clinical issues. *J Cardiovasc Med (Hagerstown)*. 2013;14:629–634. doi: 10.2459/JCM.0b013e3283629ca6
56. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, Bihorac A, Birkhahn R, Cely CM, Chawla LS, Davison DL, Feldkamp T, Forni LG, Gong MN, Gunnerson KJ, Haase M, Hackett J, Honore PM, Hoste EA, Joannes-Boyau O, Joannidis M, Kim P, Koyner JL, Laskowitz DT, Lissauer ME, Marx G, McCullough PA, Mullaney S, Ostermann M, Rimmelé T, Shapiro NI, Shaw AD, Shi J, Sprague AM, Vincent JL, Vinsonneau C, Wagner L, Walker MG, Wilkerson RG, Zacharowski K, Kellum JA. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care*. 2013;17:R25. doi: 10.1186/cc12503
57. Damman K, Ng Kam Chuen MJ, MacFadyen RJ, Lip GY, Gaze D, Collinson PO, Hillege HL, van Oeveren W, Voors AA, van Veldhuisen DJ. Volume status and diuretic therapy in systolic heart failure and the detection of early abnormalities in renal and tubular function. *J Am Coll Cardiol*. 2011;57:2233–2241. doi: 10.1016/j.jacc.2010.10.065
58. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–e161. doi: 10.1161/CIR.0000000000000509
59. McCullough PA, Duc P, Omland T, McCord J, Nowak RM, Hollander JE, Herrmann HC, Steg PG, Westheim A, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS; Breathing Not Properly Multinational Study Investigators. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. *Am J Kidney Dis*. 2003;41:571–579. doi: 10.1053/ajkd.2003.50118
60. McCullough PA, Neyou A. Comprehensive review of the relative clinical utility of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide assays in cardiovascular disease. *Open Heart Fail J*. 2009;3:6–17. doi: 10.2174/1876535100902010006
61. Palazzuoli A, Ruocco G, Pellegrini M, Martini S, Del Castillo G, Beltrami M, Franci B, Lucani B, Nuti R. Patients with cardiorenal syndrome revealed increased neurohormonal activity, tubular and myocardial damage compared to heart failure patients with preserved renal function. *Cardiorenal Med*. 2014;4:257–268. doi: 10.1159/000368375
62. Maisel AS, Daniels LB, Anand IS, McCullough PA, Chow SL. Utility of natriuretic peptides to assess and manage patients with heart failure receiving angiotensin receptor blocker/neprilysin inhibitor therapy. *Postgrad Med*. 2018;130:299–307. doi: 10.1080/00325481.2018.1440873
63. Lok DJ, Van Der Meer P, de la Porte PW, Lipsic E, Van Wijngaarden J, Hillege HL, van Veldhuisen DJ. Prognostic value of galectin-3, a novel marker of fibrosis, in patients with chronic heart failure: data from the DEAL-HF study. *Clin Res Cardiol*. 2010;99:323–328. doi: 10.1007/s00392-010-0125-y
64. McCullough PA, Olobatoke A, Vanhecke TE. Galectin-3: a novel blood test for the evaluation and management of patients with heart failure. *Rev Cardiovasc Med*. 2011;12:200–210. doi: 10.3909/ricm0624
65. van der Velde AR, Gullestad L, Ueland T, Aukrust P, Guo Y, Adourian A, Muntendam P, van Veldhuisen DJ, de Boer RA. Prognostic value of changes in galectin-3 levels over time in patients with heart failure: data from CORONA and COACH. *Circ Heart Fail*. 2013;6:219–226. doi: 10.1161/CIRCHEARTFAILURE.112.000129
66. Tang WH, Shrestha K, Shao Z, Borowski AG, Troughton RW, Thomas JD, Klein AL. Usefulness of plasma galectin-3 levels in systolic heart failure to predict renal insufficiency and survival. *Am J Cardiol*. 2011;108:385–390. doi: 10.1016/j.amjcard.2011.03.056
67. Colbert G, Jain N, de Lemos JA, Hedayati SS. Utility of traditional circulating and imaging-based cardiac biomarkers in patients with predialysis CKD. *Clin J Am Soc Nephrol*. 2015;10:515–529. doi: 10.2215/CJN.03600414
68. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz HM. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol*. 2004;43:61–67.

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69. Beigel R, Cercek B, Siegel RJ, Hamilton MA. Echo-Doppler hemodynamics: an important management tool for today's heart failure care. *Circulation*. 2015;131:1031–1034. doi: 10.1161/CIRCULATIONAHA.114.011424
70. Cowie B, Kluger R, Rex S, Missant C. Noninvasive estimation of left atrial pressure with transesophageal echocardiography. *Ann Card Anaesth*. 2015;18:312–316. doi: 10.4103/0971-9784.159799
71. Park JH, Marwick TH. Use and limitations of E/e' to assess left ventricular filling pressure by echocardiography. *J Cardiovasc Ultrasound*. 2011;19:169–173. doi: 10.4250/jcu.2011.19.4.169
72. Mavrakanas TA, Khattak A, Singh K, Charytan DM. Epidemiology and natural history of the cardiorenal syndromes in a cohort with echocardiography. *Clin J Am Soc Nephrol*. 2017;12:1624–1633. doi: 10.2215/CJN.04020417
73. Iida N, Seo Y, Sai S, Machino-Ohtsuka T, Yamamoto M, Ishizu T, Kawakami Y, Aonuma K. Clinical implications of intrarenal hemodynamic evaluation by Doppler ultrasonography in heart failure. *JACC Heart Fail*. 2016;4:674–682. doi: 10.1016/j.jchf.2016.03.016
74. Nijst P, Martens P, Dupont M, Tang WHW, Mullens W. Intrarenal flow alterations during transition from euvolemia to intravascular volume expansion in heart failure patients. *JACC Heart Fail*. 2017;5:672–681. doi: 10.1016/j.jchf.2017.05.006
75. Faubel S, Patel NU, Lockhart ME, Cadnapaphornchai MA. Renal relevant radiology: use of ultrasonography in patients with AKI. *Clin J Am Soc Nephrol*. 2014;9:382–394. doi: 10.2215/CJN.04840513
76. Edwards NC, Moody WE, Chue CD, Ferro CJ, Townend JN, Steeds RP. Defining the natural history of uremic cardiomyopathy in chronic kidney disease: the role of cardiovascular magnetic resonance. *JACC Cardiovasc Imaging*. 2014;7:703–714. doi: 10.1016/j.jcmg.2013.09.025
77. Kramann R, Erpenbeck J, Schneider RK, Röhl AB, Hein M, Brandenburg VM, van Diepen M, Dekker F, Marx N, Floege J, Becker M, Schlieper G. Speckle tracking echocardiography detects uremic cardiomyopathy early and predicts cardiovascular mortality in ESRD. *J Am Soc Nephrol*. 2014;25:2351–2365. doi: 10.1681/ASN.2013070734
78. Hassanin N, Alkemary A. Early detection of subclinical uremic cardiomyopathy using two-dimensional speckle tracking echocardiography. *Echocardiography*. 2016;33:527–536. doi: 10.1111/echo.13120
79. Krishnasamy R, Isbel NM, Hawley CM, Pascoe EM, Leano R, Haluska BA, Stanton T. The association between left ventricular global longitudinal strain, renal impairment and all-cause mortality. *Nephrol Dial Transplant*. 2014;29:1218–1225. doi: 10.1093/ndt/gfu004
80. Rutherford E, Talle MA, Mangion K, Bell E, Rauhalammi SM, Roditi G, McComb C, Radjenovic A, Welsh P, Woodward R, Struthers AD, Jardine AG, Patel RK, Berry C, Mark PB. Defining myocardial tissue abnormalities in end-stage renal failure with cardiac magnetic resonance imaging using native T1 mapping. *Kidney Int*. 2016;90:845–852. doi: 10.1016/j.kint.2016.06.014
81. Graham-Brown MP, March DS, Churchward DR, Stensel DJ, Singh A, Arnold R, Burton JO, McCann GP. Novel cardiac nuclear magnetic resonance method for noninvasive assessment of myocardial fibrosis in hemodialysis patients. *Kidney Int*. 2016;90:835–844. doi: 10.1016/j.kint.2016.07.014
82. Parrinello G, Paterna S, Di Pasquale P, Torres D, Fatta A, Mezzero M, Scaglione R, Licata G. The usefulness of bioelectrical impedance analysis in differentiating dyspnea due to decompensated heart failure. *J Card Fail*. 2008;14:676–686. doi: 10.1016/j.cardfail.2008.04.005
83. Piccoli A, Codognotto M, Cianci V, Vettore G, Zaninotto M, Plebani M, Maisel A, Peacock WF. Differentiation of cardiac and noncardiac dyspnea using bioelectrical impedance vector analysis (BIVA). *J Card Fail*. 2012;18:226–232. doi: 10.1016/j.cardfail.2011.11.001
84. Valle R, Aspromonte N, Giovinazzo P, Carbonieri E, Chiatto M, di Tano G, Feola M, Milli M, Fontebasso A, Barro S, Bardellotto S, Milani L. B-type natriuretic peptide-guided treatment for predicting outcome in patients hospitalized in sub-intensive care unit with acute heart failure. *J Card Fail*. 2008;14:219–224. doi: 10.1016/j.cardfail.2007.10.009
85. Valle R, Aspromonte N, Milani L, Peacock FW, Maisel AS, Santini M, Ronco C. Optimizing fluid management in patients with acute decompensated heart failure (ADHF): the emerging role of combined measurement of body hydration status and brain natriuretic peptide (BNP) levels. *Heart Fail Rev*. 2011;16:519–529. doi: 10.1007/s10741-011-9244-4
86. Di Somma S, Lalle I, Magrini L, Russo V, Navarin S, Castello L, Avanzi GC, Di Stasio E, Maisel A. Additive diagnostic and prognostic value of bioelectrical impedance vector analysis (BIVA) to brain natriuretic peptide "grey-zone" in patients with acute heart failure in the emergency department. *Eur Heart J Acute Cardiovasc Care*. 2014;3:167–175. doi: 10.1177/2048872614521756
87. Santarelli S, Russo V, Lalle I, De Berardinis B, Navarin S, Magrini L, Piccoli A, Codognotto M, Castello LM, Avanzi GC, Villacorta H, Precht BLC, de Araújo Porto PB, Villacorta AS, Di Somma S; Great Network. Usefulness of combining admission brain natriuretic peptide (BNP) plus hospital discharge bioelectrical impedance vector analysis (BIVA) in predicting 90 days cardiovascular mortality in patients with acute heart failure. *Intern Emerg Med*. 2017;12:445–451. doi: 10.1007/s11739-016-1581-9
88. Zoccali C, Moissl U, Chazot C, Mallamaci F, Tripepi G, Arkossy O, Wabel P, Stuard S. Chronic fluid overload and mortality in ESRD. *J Am Soc Nephrol*. 2017;28:2491–2497. doi: 10.1681/ASN.2016121341
89. Hasper D, Jörres A. New insights into the management of hepatorenal syndrome. *Liver Int*. 2011;31(suppl 3):27–30. doi: 10.1111/j.1478-3231.2011.02586.x
90. Miller WL, Mullan BP. Understanding the heterogeneity in volume overload and fluid distribution in decompensated heart failure is key to optimal volume management: role for blood volume quantitation. *JACC Heart Fail*. 2014;2:298–305. doi: 10.1016/j.jchf.2014.02.007
91. Givertz MM, Stevenson LW, Costanzo MR, Bourge RC, Bauman JG, Ginn G, Abraham WT; CHAMPION Trial Investigators. Pulmonary artery pressure-guided management of patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2017;70:1875–1886. doi: 10.1016/j.jacc.2017.08.010
92. Yamokoski LM, Haas GJ, Gans B, Abraham WT. OptiVol fluid status monitoring with an implantable cardiac device: a heart failure management system. *Expert Rev Med Devices*. 2007;4:775–780. doi: 10.1586/17434440.4.6.775
93. Zile MR, Sharma V, Johnson JW, Warman EN, Baicu CF, Bennett TD. Prediction of all-cause mortality based on the direct measurement of intrathoracic impedance. *Circ Heart Fail*. 2016;9:e002543. doi: 10.1161/CIRCHEARTFAILURE.115.002543
94. Domenichini G, Rahneva T, Diab IG, Dhillon OS, Campbell NG, Finlay MC, Baker V, Hunter RJ, Earley MJ, Schilling RJ. The Lung Impedance Monitoring in Treatment of Chronic Heart Failure (the LIMIT-CHF study). *Europace*. 2016;18:428–435. doi: 10.1093/europace/euv293
95. van Veldhuisen DJ, Braunschweig F, Conraads V, Ford I, Cowie MR, Jondeau G, Kautzner J, Aguilera RM, Lunati M, Yu CM, Gerritse B, Borggrefe M; for the DOT-HF Investigators. Intrathoracic impedance monitoring, audible patient alerts, and outcome in patients with heart failure. *Circulation*. 2011;124:1719–1726. doi: 10.1161/CIRCULATIONAHA.111.043042
96. Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, Stevenson LW, Francis GS, Leier CV, Miller LW; ESCAPE Investigators and ESCAPE Study Coordinators. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA*. 2005;294:1625–1633. doi: 10.1001/jama.294.13.1625
97. Grodin JL, Drazner MH, Dupont M, Mullens W, Taylor DO, Starling RC, Tang WH. A disproportionate elevation in right ventricular filling pressure, in relation to left ventricular filling pressure, is associated with renal impairment and increased mortality in advanced decompensated heart failure. *Am Heart J*. 2015;169:806–812. doi: 10.1016/j.ahj.2015.02.017
98. Titze J, Bauer K, Schafflhuber M, Dietsch P, Lang R, Schwind KH, Luft FC, Eckardt KU, Hilgers KF. Internal sodium balance in DOCA-salt rats: a body composition study. *Am J Physiol Renal Physiol*. 2005;289:F793–F802. doi: 10.1152/ajprenal.00096.2005
99. Dahlmann A, Dörfelt K, Eicher F, Linz P, Kopp C, Mössinger I, Horn S, Büschges-Seraphin B, Wabel P, Hammon M, Cavallaro A, Eckardt KU, Kotanko P, Levin NW, Johannes B, Uder M, Luft FC, Müller DN, Titze JM. Magnetic resonance-determined sodium removal from tissue stores in hemodialysis patients. *Kidney Int*. 2015;87:434–441. doi: 10.1038/ki.2014.269
100. Hammon M, Grossmann S, Linz P, Kopp C, Dahlmann A, Garlichs C, Janka R, Cavallaro A, Luft FC, Uder M, Titze J. ^{23}Na magnetic resonance imaging of the lower leg of acute heart failure patients during diuretic treatment. *PLoS One*. 2015;10:e0141336. doi: 10.1371/journal.pone.0141336
101. Fonarow GC, Heywood JT, Heidenreich PA, Lopatin M, Yancy CW; ADHERE Scientific Advisory Committee and Investigators. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J*. 2007;153:1021–1028. doi: 10.1016/j.ahj.2007.03.012
102. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. *Cochrane Database Syst Rev*. 2012:CD003838.
103. Felker GM, O'Connor CM, Braunwald E; for the Heart Failure Clinical Research Network Investigators. Loop diuretics in acute decompensated

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heart failure: necessary? Evil? A necessary evil? *Circ Heart Fail*. 2009;2:56–62. doi: 10.1161/CIRCHEARTFAILURE.108.821785
104. Sica DA. Pharmacotherapy in congestive heart failure: drug absorption in the management of congestive heart failure: loop diuretics. *Congest Heart Fail*. 2003;9:287–292.
105. Gilotra NA, Princewill O, Marino B, Okwuosa IS, Chasler J, Almansa J, Cummings A, Rhodes P, Chambers J, Cuomo K, Russell SD. Efficacy of intravenous furosemide versus a novel, pH-neutral furosemide formulation administered subcutaneously in outpatients with worsening heart failure. *JACC Heart Fail*. 2018;6:65–70. doi: 10.1016/j.jchf.2017.10.001
106. Rangaswami J, McCullough PA. Efficacy of subcutaneous versus intravenous administration of furosemide in patients with worsening heart failure: the devil is in the details. *JACC Heart Fail*. 2018;6:266–267. doi: 10.1016/j.jchf.2018.01.010
107. Brater DC. Pharmacology of diuretics. *Am J Med Sci*. 2000;319:38–50.
108. Shah S, Pitt B, Brater DC, Feig PU, Shen W, Khwaja FS, Wilcox CS. Sodium and fluid excretion with torsemide in healthy subjects is limited by the short duration of diuretic action. *JAHA*. 2017;6:e006135. doi: 10.1161/JAHA.117.006135
109. Cosín J, Díez J; TORIC Investigators. Torasemide in chronic heart failure: results of the TORIC study. *Eur J Heart Fail*. 2002;4:507–513.
110. DiNicolantonio JJ. Should torsemide be the loop diuretic of choice in systolic heart failure? *Future Cardiol*. 2012;8:707–728. doi: 10.2217/fca.12.54
111. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. *J Am Coll Cardiol*. 2012;60:1031–1042. doi: 10.1016/j.jacc.2012.01.077
112. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J*. 2014;35:455–469. doi: 10.1093/eurheartj/eht386
113. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM; NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364:797–805. doi: 10.1056/NEJMoa1005419
114. Palazzuoli A, Pellegrini M, Ruocco G, Martini G, Franci B, Campagna MS, Gilleman M, Nuti R, McCullough PA, Ronco C. Continuous versus bolus intermittent loop diuretic infusion in acutely decompensated heart failure: a prospective randomized trial. *Crit Care*. 2014;18:R134. doi: 10.1186/cc13952
115. Grodin JL, Stevens SR, de Las Fuentes L, Kiernan M, Birati EY, Gupta D, Bart BA, Felker GM, Chen HH, Butler J, Dávila-Román VG, Margulies KB, Hernandez AF, Anstrom KJ, Tang WH. Intensification of medication therapy for cardiorenal syndrome in acute decompensated heart failure. *J Card Fail*. 2016;22:26–32. doi: 10.1016/j.cardfail.2015.07.007
116. Chen HH, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ, Goldsmith SR, Bart BA, Bull DA, Stehlik J, LeWinter MM, Konstam MA, Huggins GS, Rouleau JL, O'Meara E, Tang WH, Starling RC, Butler J, Deswal A, Felker GM, O'Connor CM, Bonita RE, Margulies KB, Cappola TP, Ofili EO, Mann DL, Dávila-Román VG, McNulty SE, Borlaug BA, Velazquez EJ, Lee KL, Shah MR, Hernandez AF, Braunwald E, Redfield MM; NHLBI Heart Failure Clinical Research Network. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA*. 2013;310:2533–2543. doi: 10.1001/jama.2013.282190
117. Mentz RJ, Stevens SR, DeVore AD, Lala A, Vader JM, AbouEzzeddine OF, Khazanie P, Redfield MM, Stevenson LW, O'Connor CM, Goldsmith SR, Bart BA, Anstrom KJ, Hernandez AF, Braunwald E, Felker GM. Decongestion strategies and renin-angiotensin-aldosterone system activation in acute heart failure. *JACC Heart Fail*. 2015;3:97–107. doi: 10.1016/j.jchf.2014.09.003
118. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison B, Cleland JG, Givertz MM, Bloomfield DM, Fiuzat M, Dittrich HC, Hillege HL. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. *Eur Heart J*. 2014;35:1284–1293. doi: 10.1093/eurheartj/ehu065
119. ter Maaten JM, Dunning AM, Valente MA, Damman K, Ezekowitz JA, Califf RM, Starling RC, van der Meer P, O'Connor CM, Schulte PJ, Testani JM, Hernandez AF, Tang WH, Voors AA. Diuretic response in acute heart failure: an analysis from ASCEND-HF. *Am Heart J*. 2015;170:313–321. doi: 10.1016/j.ahj.2015.05.003
120. Brater DC. Diuretic therapy. *N Engl J Med*. 1998;339:387–395. doi: 10.1056/NEJM199808063390607
121. Bard RL, Bleske BE, Nicklas JM. Food: an unrecognized source of loop diuretic resistance. *Pharmacotherapy*. 2004;24:630–637.
122. Rudy DW, Gehr TW, Matzke GR, Kramer WG, Sica DA, Brater DC. The pharmacodynamics of intravenous and oral torsemide in patients with chronic renal insufficiency. *Clin Pharmacol Ther*. 1994;56:39–47.
123. Gehr TW, Rudy DW, Matzke GR, Kramer WG, Sica DA, Brater DC. The pharmacokinetics of intravenous and oral torsemide in patients with chronic renal insufficiency. *Clin Pharmacol Ther*. 1994;56:31–38.
124. Marumo R, Kaizuma S, Nogae S, Kanazawa M, Kimura T, Saito T, Ito S, Matsubara M. Differential upregulation of rat Na-K-Cl cotransporter, rBSC1, mRNA in the thick ascending limb of Henle in different pathological conditions. *Kidney Int*. 1998;54:877–888. doi: 10.1046/j.1523-1755.1998.00051.x
125. Wilcox CS, Mitch WE, Kelly RA, Skorecki K, Meyer TW, Friedman PA, Souney PF. Response of the kidney to furosemide, I: effects of salt intake and renal compensation. *J Lab Clin Med*. 1983;102:450–458.
126. Rao VS, Planavsky N, Hanberg JS, Ahmad T, Brisco-Bacik MA, Wilson FP, Jacoby D, Chen M, Tang WHW, Cherney DZI, Ellison DH, Testani JM. Compensatory distal reabsorption drives diuretic resistance in human heart failure. *J Am Soc Nephrol*. 2017;28:3414–3424. doi: 10.1681/ASN.2016111178
127. Ter Maaten JM, Rao VS, Hanberg JS, Perry Wilson F, Bellumkonda L, Assefa M, Sam Broughton J, D'Ambrosi J, Wilson Tang WH, Damman K, Voors AA, Ellison DH, Testani JM. Renal tubular resistance is the primary driver for loop diuretic resistance in acute heart failure. *Eur J Heart Fail*. 2017;19:1014–1022. doi: 10.1002/ejhf.757
128. Butler J, Anstrom KJ, Felker GM, Givertz MM, Kalogeropoulos AP, Konstam MA, Mann DL, Margulies KB, McNulty SE, Mentz RJ, Redfield MM, Tang WHW, Whellan DJ, Shah M, Desvigne-Nickens P, Hernandez AF, Braunwald E; National Heart Lung and Blood Institute Heart Failure Clinical Research Network. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. *JAMA Cardiol*. 2017;2:950–958. doi: 10.1001/jamacardio.2017.2198
129. Hanberg JS, Rao V, Ter Maaten JM, Laur O, Brisco MA, Perry Wilson F, Grodin JL, Assefa M, Samuel Broughton J, Planavsky NJ, Ahmad T, Bellumkonda L, Tang WH, Parikh CR, Testani JM. Hypochloremia and diuretic resistance in heart failure: mechanistic insights. *Circ Heart Fail*. 2016;9:e003180. doi: 10.1161/CIRCHEARTFAILURE.116.003180
130. Testani JM, Brisco MA, Turner JM, Spatz ES, Bellumkonda L, Parikh CR, Tang WH. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. *Circ Heart Fail*. 2014;7:261–270. doi: 10.1161/CIRCHEARTFAILURE.113.000895
131. Singh D, Shrestha K, Testani JM, Verbrugge FH, Dupont M, Mullens W, Tang WH. Insufficient natriuretic response to continuous intravenous furosemide is associated with poor long-term outcomes in acute decompensated heart failure. *J Card Fail*. 2014;20:392–399. doi: 10.1016/j.cardfail.2014.03.006
132. Ali SS, Olinger CC, Sobotka PA, Dahle TG, Bunte MC, Blake D, Boyle AJ. Loop diuretics can cause clinical natriuretic failure: a prescription for volume expansion. *Congest Heart Fail*. 2009;15:1–4. doi: 10.1111/j.1751-7133.2008.00037.x
133. Bart BA, Boyle A, Bank AJ, Anand I, Olivari MT, Kraemer M, Mackedanz S, Sobotka PA, Schollmeyer M, Goldsmith SR. Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial. *J Am Coll Cardiol*. 2005;46:2043–2046.
134. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, Jaski BE, Fang JC, Feller ED, Haas GJ, Anderson AS, Schollmeyer MP, Sobotka PA. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol*. 2007;49:675–683.
135. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E; Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012;367:2296–2304. doi: 10.1056/NEJMoa1210357
136. Marenzi G, Muratori M, Cosentino ER, Rinaldi ER, Donghi V, Milazzo V, Ferramosca E, Borghi C, Santoro A, Agostini P. Continuous ultrafiltration

Downloaded from http://ahajournals.org by on October 10, 2025

for congestive heart failure: the CUORE trial. *J Card Fail*. 2014;20:9–17. doi: 10.1016/j.cardfail.2013.11.004
137. Costanzo MR, Negoianu D, Jaski BE, Bart BA, Heywood JT, Anand IS, Smelser JM, Kaneshige AM, Chomsky DB, Adler ED, Haas GJ, Watts JA, Nabut JL, Schollmeyer MP, Fonarow GC. Aquapheresis versus intravenous diuretics and hospitalizations for heart failure. *JACC Heart Fail*. 2016;4:95–105.
138. Marenzi G, Lauri G, Grazi M, Assanelli E, Campodonico J, Agostoni P. Circulatory response to fluid overload removal by extracorporeal ultrafiltration in refractory congestive heart failure. *J Am Coll Cardiol*. 2001;38:963–968.
139. Manning M, Sawyer WH. Discovery, development, and some uses of vasopressin and oxytocin antagonists. *J Lab Clin Med*. 1989;114:617–632.
140. Gheorghiade M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA*. 2007;297:1332–1343. doi: 10.1001/jama.297.12.1332
141. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA*. 2007;297:1319–1331. doi: 10.1001/jama.297.12.1319
142. Felker GM, Mentz RJ, Cole RT, Adams KF, Egnaczyk GF, Fiuzat M, Patel CB, Echols M, Khouri MG, Tauras JM, Gupta D, Monds P, Roberts R, O'Connor CM. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. *J Am Coll Cardiol*. 2017;69:1399–1406. doi: 10.1016/j.jacc.2016.09.004
143. Konstam MA, Kiernan M, Chandler A, Dhingra R, Mody FV, Eisen H, Haught WH, Wagoner L, Gupta D, Patten R, Gordon P, Korr K, Fileccia R, Pressler SJ, Gregory D, Wedge P, Dowling D, Romeling M, Konstam JM, Massaro JM, Udelson JE; SECRET of CHF Investigators, Coordinators, and Committee Members. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. *J Am Coll Cardiol*. 2017;69:1409–1419. doi: 10.1016/j.jacc.2016.12.035
144. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA*. 2002;287:1531–40.
145. Jensen KT, Carstens J, Pedersen EB. Effect of BNP on renal hemodynamics, tubular function and vasoactive hormones in humans. *Am J Physiol*. 1998;274(pt 2):F63–F72.
146. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JJ, Nieminen MS, Reist CJ, Rouleau JL, Swedberg K, Adams KF Jr, Anker SD, Atar D, Battler A, Botero R, Bohidar NR, Butler J, Clausell N, Corbalán R, Costanzo MR, Dahlstrom U, Deckelbaum LI, Diaz R, Dunlap ME, Ezekowitz JA, Feldman D, Felker GM, Fonarow GC, Gennevois D, Gottlieb SS, Hill JA, Hollander JE, Howlett JG, Hudson MP, Kociol RD, Krum H, Laucevicius A, Levy WC, Méndez GF, Metra M, Mittal S, Oh BH, Pereira NL, Ponikowski P, Tang WH, Wilson WH, Tanomsup S, Teerlink JR, Triposkiadis F, Troughton RW, Voors AA, Whellan DJ, Zannad F, Califf RM. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med*. 2011;365:32–43. doi: 10.1056/NEJMoa1100171
147. Hasenfuss G, Teerlink JR. Cardiac inotropes: current agents and future directions. *Eur Heart J*. 2011;32:1838–1845. doi: 10.1093/eurheartj/ehr026
148. Goldberg LI. Pharmacological bases for the use of dopamine and related drugs in the treatment of congestive heart failure. *J Cardiovasc Pharmacol*. 1989;14(suppl 8):S21–S28.
149. Friedrich JO, Adhikari N, Herridge MS, Beyene J. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med*. 2005;142:510–524.
150. Wan SH, Stevens SR, Borlaug BA, Anstrom KJ, Deswal A, Felker GM, Givertz MM, Bart BA, Tang WH, Redfield MM, Chen HH. Differential response to low-dose dopamine or low-dose nesiritide in acute heart failure with reduced or preserved ejection fraction: results from the ROSE AHF trial (Renal Optimization Strategies Evaluation in Acute Heart Failure). *Circ Heart Fail*. 2016;9:e002593. doi: 10.1161/CIRCHEARTFAILURE.115.002593
151. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation*. 2004;109:1004–1009. doi: 10.1161/01.CIR.0000116764.53225.A9
152. Frances CD, Noguchi H, Massie BM, Browner WS, McClellan M. Are we inhibited? Renal insufficiency should not preclude the use of ACE inhibitors for patients with myocardial infarction and depressed left ventricular function. *Arch Intern Med*. 2000;160:2645–2650.
153. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987;316:1429–1435.
154. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325:293–302.
155. Khan NA, Ma I, Thompson CR, Humphries K, Salem DN, Sarnak MJ, Levin A. Kidney function and mortality among patients with left ventricular systolic dysfunction. *J Am Soc Nephrol*. 2006;17:244–253. doi: 10.1681/ASN.2005030270
156. de Denus S, Tardif JC, White M, Bourassa MG, Racine N, Levesque S, Ducharme A. Quantification of the risk and predictors of hyperkalemia in patients with left ventricular dysfunction: a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trials. *Am Heart J*. 2006;152:705–712. doi: 10.1016/j.ahj.2006.05.030
157. Flather MD, Yusuf S, Køber L, Pfeffer M, Hall A, Murray G, Torp-Pedersen C, Ball S, Pogue J, Moyé L, Braunwald E. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients: ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet*. 2000;355:1575–1581.
158. Hiremath S, Fergusson DA, Fergusson N, Bennett A, Knoll GA. Renin-Angiotensin system blockade and long-term clinical outcomes in kidney transplant recipients: a meta-analysis of randomized controlled trials. *Am J Kidney Dis*. 2017;69:78–86. doi: 10.1053/j.ajkd.2016.08.018
159. Ahmed A, Fonarow GC, Zhang Y, Sanders PW, Allman RM, Arnett DK, Feller MA, Love TE, Aban IB, Levesque R, Ekundayo OJ, Dell'Italia LJ, Bakris GL, Rich MW. Renin-angiotensin inhibition in systolic heart failure and chronic kidney disease. *Am J Med*. 2012;125:399–410. doi: 10.1016/j.amjmed.2011.10.013
160. Swedberg K, Kjekshus J. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *Am J Cardiol*. 1988;62:60A–66A.
161. Kjekshus J, Swedberg K. Enalapril for congestive heart failure. *Am J Cardiol*. 1989;63:D26–D32.
162. Swedberg K, Eneroth P, Kjekshus J, Snapinn S. Effects of enalapril and neuroendocrine activation on prognosis in severe congestive heart failure (follow-up of the CONSENSUS trial). *Am J Cardiol*. 1990;66:D40–D45.
163. Bowling CB, Sanders PW, Allman RM, Rogers WJ, Patel K, Aban IB, Rich MW, Pitt B, White M, Bakris GC, Fonarow GC, Ahmed A. Effects of enalapril in systolic heart failure patients with and without chronic kidney disease: insights from the SOLVD Treatment trial. *Int J Cardiol*. 2013;167:151–156. doi: 10.1016/j.ijcard.2011.12.056
164. SOLVD Investigators, Yusuf S, Pitt B, David CE, Hood WB Jr, Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med*. 1992;327:685–691.
165. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial: the SAVE Investigators. *N Engl J Med*. 1992;327:669–677.
166. Tokmakova MP, Skali H, Kenchaiah S, Braunwald E, Rouleau JL, Packer M, Chertow GM, Moye LA, Pfeffer MA, Solomon SD. Chronic kidney disease, cardiovascular risk, and response to angiotensin-converting enzyme inhibition after myocardial infarction: the Survival and Ventricular Enlargement (SAVE) Study. *Circulation*. 2004;110:3667–3673. doi: 10.1161/01.CIR.0000149806.01354.BF
167. Massie BM, Armstrong PW, Cleland JF, Horowitz JD, Packer M, Poole-Wilson PA, Rydén L. Toleration of high doses of angiotensin-converting enzyme inhibitors in patients with chronic heart failure: results from the ATLAS trial. *Arch Intern Med*. 2001;161:165–171.
168. Ahmed A, Love TE, Sui X, Rich MW. Effects of angiotensin-converting enzyme inhibitors in systolic heart failure patients with chronic kidney disease: a propensity score analysis. *J Card Fail*. 2006;12:499–506.
169. Berger AK, Duval S, Manske C, Vazquez G, Barber C, Miller L, Luepker RV. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with congestive heart failure and chronic kidney disease. *Am Heart J*. 2007;153:1064–1073.

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170. Ahmed A, Rich MW, Zile M, Sanders PW, Patel K, Zhang Y, Aban IB, Love TE, Fonarow GC, Aronow WS, Allman RM. Renin-angiotensin inhibition in diastolic heart failure and chronic kidney disease. *Am J Med*. 2013;126:150–161. doi: 10.1016/j.amjmed.2012.06.031
171. Edner M, Benson L, Dahlstrom U, Lund LH. Association between renin-angiotensin system antagonist use and mortality in heart failure with severe renal insufficiency: a prospective propensity score-matched cohort study. *Eur Heart J*. 2015;36:2318–2326. doi: 10.1093/eurheartj/ehv268
172. Gurwitz JH, Magid DJ, Smith DH, Tabada GH, Sung SH, Allen LA, McManus DD, Goldberg RJ, Tisminetzky M, Go AS. Treatment effectiveness in heart failure with comorbidity: lung disease and kidney disease. *J Am Geriatr Soc*. 2017;65:2610–2618.
173. Desai AS, Swedberg K, McMurray JJV, Granger CB, Yusuf S, Young JB, Dunlap ME, Solomon SD, Hainer JW, Olofsson B, Michelson EL, Pfeffer MA; CHARM Program Investigators. Incidence and predictors of hyperkalemia in patients with heart failure: an analysis of the CHARM Program. *J Am Coll Cardiol*. 2007;50:1959–1966.
174. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, Riegger GA, Malbecq W, Smith RD, Guptha S, Poole-Wilson PA; HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet*. 2009;374:1840–1848. doi: 10.1016/S0140-6736(09)61913-9
175. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania PC, Ney DE, Snavely DB, Chang PI. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet*. 1997;349:747–752.
176. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2010;121:e258]. *Circulation*. 2009;119:e391–e479. doi: 10.1161/CIRCULATIONAHA.109.192065
177. Solomon SD, Claggett B, McMurray JJ, Hernandez AF, Fonarow GC. Combined neprilysin and renin-angiotensin system inhibition in heart failure with reduced ejection fraction: a meta-analysis. *Eur J Heart Fail*. 2016;18:1238–1243. doi: 10.1002/ejhf.603
178. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ; Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*. 2012;380:1387–1395. doi: 10.1016/S0140-6736(12)61227-6
179. Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, Prescott MF, Shi VC, Rouleau JL, Swedberg K, Zile MR, Packer M, Desai AS, Solomon SD, McMurray JV. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. *JACC Heart Fail*. 2018;6:489–498. doi: 10.1016/j.jchf.2018.02.004
180. UK HARP-III Collaborative Group. Randomized multicentre pilot study of sacubitril/valsartan versus irbesartan in patients with chronic kidney disease: United Kingdom Heart and Renal Protection (HARP), III: rationale, trial design and baseline data. *Nephrol Dial Transplant*. 2017;32:2043–2051. doi: 10.1093/ndt/gfw321
181. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure: Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709–717. doi: 10.1056/NEJM199909023411001
182. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309–1321. doi: 10.1056/NEJMoa030207
183. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11–21. doi: 10.1056/NEJMoa1009492
184. Vardeny O, Wu DH, Desai A, Rossignol P, Zannad F, Pitt B, Solomon SD; RALES Investigators. Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). *J Am Coll Cardiol*. 2012;60:2082–2089. doi: 10.1016/j.jacc.2012.07.048
185. Eschalier R, McMurray JJV, Swedberg K, van Veldhuisen DJ, Krum H, Pocock SJ, Shi H, Vincent J, Rossignol P, Zannad F, Pitt B; EMPHASIS-HF Investigators. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure). *J Am Coll Cardiol*. 2013;62:1585–1593. doi: 10.1016/j.jacc.2013.04.086
186. Filippatos G, Anker SD, Bohm M, Gheorghiade M, Kober L, Krum H, Maggioni AP, Ponikowski P, Voors AA, Zannad F, Kim SY, Nowack C, Palombo G, Kolkhof P, Kimmeskamp-Kirschbaum N, Pieper A, Pitt B. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. *Eur Heart J*. 2016;37:2105–2114.
187. Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, Bushinsky DA. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. *Am J Nephrol*. 2017;46:213–221. doi: 10.1159/000479802
188. Vukadinović D, Lavall D, Vukadinović AN, Pitt B, Wagenpfeil S, Böhm M. True rate of mineralocorticoid receptor antagonists-related hyperkalemia in placebo-controlled trials: a meta-analysis. *Am Heart J*. 2017;188:99–108. doi: 10.1016/j.ahj.2017.03.011
189. McCullough PA, Costanzo MR, Silver M, Spinowitz B, Zhang J, Lepor NE. Novel agents for the prevention and management of hyperkalemia. *Rev Cardiovasc Med*. 2015;16:140–155.
190. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128:1810–1852. doi: 10.1161/CIR.0b013e31829e8807
191. Ghali JK, Wikstrand J, Van Veldhuisen DJ, Fagerberg B, Goldstein S, Hjalmarson A, Johansson P, Kjekshus J, Ohlsson L, Samuelsson O, Waagstein F, Wedel H; MERIT-HF Study Group. The influence of renal function on clinical outcome and response to beta-blockade in systolic heart failure: insights from Metoprolol CR/XL Randomized Intervention Trial in Chronic HF (MERIT-HF). *J Card Fail*. 2009;15:310–318. doi: 10.1016/j.cardfail.2008.11.003
192. Cohen-Solal A, Kotecha D, van Veldhuisen DJ, Babalis D, Böhm M, Coats AJ, Roughton M, Poole-Wilson P, Tavazzi L, Flather M; SENIORS Investigators. Efficacy and safety of nebivolol in elderly heart failure patients with impaired renal function: insights from the SENIORS trial. *Eur J Heart Fail*. 2009;11:872–880. doi: 10.1093/eurjhf/hfp104
193. Castagno D, Jhund PS, McMurray JJ, Lewsey JD, Erdmann E, Zannad F, Remme WJ, Lopez-Sendon JL, Lechat P, Follath F, Höglund C, Mareev V, Sadowski Z, Seabra-Gomes RJ, Dargie HJ. Improved survival with bisoprolol in patients with heart failure and renal impairment: an analysis of the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) trial. *Eur J Heart Fail*. 2010;12:607–616. doi: 10.1093/eurjhf/hfq038
194. Badve SV, Roberts MA, Hawley CM, Cass A, Garg AX, Krum H, Tonkin A, Perkovic V. Effects of beta-adrenergic antagonists in patients with chronic kidney disease: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2011;58:1152–1161. doi: 10.1016/j.jacc.2011.04.041
195. Damman K, Tang WH, Felker GM, Lassus J, Zannad F, Krum H, McMurray JJ. Current evidence on treatment of patients with chronic systolic heart failure and renal insufficiency: practical considerations from published data. *J Am Coll Cardiol*. 2014;63:853–871. doi: 10.1016/j.jacc.2013.11.031
196. Dailey G. Overall mortality in diabetes mellitus: where do we stand today? *Diabetes Technol Ther*. 2011;13(suppl 1):S65–S74. doi: 10.1089/dia.2011.0019
197. Claesen M, Gillard P, De Smet F, Callens M, De Moor B, Mathieu C. Mortality in individuals treated with glucose-lowering agents: a large, controlled cohort study. *J Clin Endocrinol Metab*. 2016;101:461–469. doi: 10.1210/jc.2015-3184
198. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia*. 2015;58:429–442. doi: 10.1007/s00125-014-3460-0

Downloaded from http://ahajournals.org by on October 10, 2025

199. Standards of medical care in diabetes–2018. *Diabetes Care*. 2018; 41(suppl 1):S1–S159.
200. Rocha NA, McCullough PA. Cardiovascular outcomes in diabetic kidney disease: insights from recent clinical trials. *Kidney Int Suppl (2011)*. 2018;8:8–17. doi: 10.1016/j.kisu.2017.10.004
201. Udell JA, Cavender MA, Bhatt DL, Chatterjee S, Farkouh ME, Scirica BM. Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol*. 2015;3:356–366. doi: 10.1016/S2213-8587(15)00044-3
202. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128. doi: 10.1056/NEJMoa1504720
203. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375:323–334. doi: 10.1056/NEJMoa1515920
204. Wanner C. EMPA-REG OUTCOME: the nephrologist's point of view. *Am J Cardiol*. 2017;120:S59–S67. doi: 10.1016/j.amjcard.2017.05.012
205. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657. doi: 10.1056/NEJMoa1611925
206. US Food and Drug Administration. Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes with the diabetes medicine canagliflozin (Invokana, Invokamet); FDA to investigate. 2016. https://www.fda.gov/Drugs/DrugSafety/ucm500965.htm. Accessed February 15, 2018.
207. Verma S, Mazer CD, Al-Omran M, Inzucchi SE, Fitchett D, Hehnke U, George JT, Zinman B. Cardiovascular outcomes and safety of empagliflozin in patients with type 2 diabetes mellitus and peripheral artery disease: a subanalysis of EMPA-REG OUTCOME. *Circulation*. 2018;137:405–407. doi: 10.1161/CIRCULATIONAHA.117.032031
208. Baartscheer A, Schumacher CA, Wüst RC, Fiolet JW, Stienen GJ, Coronel R, Zuurbier CJ. Empagliflozin decreases myocardial cytoplasmic Na^+ through inhibition of the cardiac Na^+/H^+ exchanger in rats and rabbits. *Diabetologia*. 2017;60:568–573. doi: 10.1007/s00125-016-4134-x
209. Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, Norhammar A, Birkeland KI, Jørgensen ME, Thuresson M, Arya N, Bodegård J, Hammar N, Fenici P; on behalf of the CVD-REAL Investigators and Study Group. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). *Circulation*. 2017;136:249–259. doi: 10.1161/CIRCULATIONAHA.117.029190
210. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368:1696–1705. doi: 10.1016/S0140-6736(06)69705-5
211. Mann JFE, Ørsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, Tornøe K, Zinman B, Buse JB; LEADER Steering Committee and Investigators. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med*. 2017;377:839–848. doi: 10.1056/NEJMoa1616011
212. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834–1844. doi: 10.1056/NEJMoa1607141
213. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, Maggioni AP, Marso SP, Öhman P, Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017;377:1228–1239. doi: 10.1056/NEJMoa1612917
214. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373:2247–2257. doi: 10.1056/NEJMoa1509225
215. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369:1317–1326. doi: 10.1056/NEJMoa1307684
216. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369:1327–1335. doi: 10.1056/NEJMoa1305889
217. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373:232–242. doi: 10.1056/NEJMoa1501352
218. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, Udell JA, Mosenzon O, Im K, Umez-Eronini AA, Pollack PS, Hirshberg B, Frederich R, Lewis BS, McGuire DK, Davidson J, Steg PG, Bhatt DL; for the SAVOR-TIMI 53 Steering Committee and Investigators. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation*. 2014;130:1579–1588. doi: 10.1161/CIRCULATIONAHA.114.010389
219. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Lam H, White WB; EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet*. 2015;385:2067–2076. doi: 10.1016/S0140-6736(14)62225-X
220. McGuire DK, Van de Werf F, Armstrong PW, Standl E, Koglin J, Green JB, Bethel MA, Cornel JH, Lopes RD, Halvorsen S, Ambrosio G, Buse JB, Josse RG, Lachin JM, Pencina MJ, Garg J, Lokhnygina Y, Holman RR, Peterson ED Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) Study Group. Association between sitagliptin use and heart failure hospitalization and related outcomes in type 2 diabetes mellitus: secondary analysis of a randomized clinical trial. *JAMA Cardiol*. 2016;1:126–135. doi: 10.1001/jamacardio.2016.0103
221. Schernthaner G, Cahn A, Raz I. Is the use of DPP-4 inhibitors associated with an increased risk for heart failure? Lessons from EXAMINE, SAVOR-TIMI 53, and TECOS. *Diabetes Care*. 2016;39(suppl 2):S210–S218. doi: 10.2337/dcS15-3009
222. Mentz RJ, Kelly JP, von Lueder TG, Voors AA, Lam CS, Cowie MR, Kjeldsen K, Jankowska EA, Atar D, Butler J, Fiuzat M, Zannad F, Pitt B, O'Connor CM. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol*. 2014;64:2281–2293. doi: 10.1016/j.jacc.2014.08.036
223. Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, Whelton PK, He J. The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med*. 2004;140:167–174.
224. Russo AM, Stainback RF, Bailey SR, Epstein AE, Heidenreich PA, Jessup M, Kapa S, Kremers MS, Lindsay BD, Stevenson LW. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation appropriate use criteria task force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *Heart Rhythm*. 2013;10:e11–e58. doi: 10.1016/j.hrthm.2013.01.008
225. Sakhuja R, Keebler M, Lai TS, McLaughlin Gavin C, Thakur R, Bhatt DL. Meta-analysis of mortality in dialysis patients with an implantable cardioverter defibrillator. *Am J Cardiol*. 2009;103:735–741. doi: 10.1016/j.amjcard.2008.11.014
226. Cuculich PS, Sánchez JM, Kerzner R, Greenberg SL, Sengupta J, Chen J, Faddis MN, Gleva MJ, Smith TW, Lindsay BD. Poor prognosis for patients with chronic kidney disease despite ICD therapy for the primary prevention of sudden death. *Pacing Clin Electrophysiol*. 2007;30:207–213. doi: 10.1111/j.1540-8159.2007.00651.x
227. Vachharajani TJ, Salman L, Costanzo EJ, Mehandru SK, Patel M, Calderon DM, Mathew RO, Sidhu MS, Asif A. Subcutaneous defibrillators for dialysis patients. *Hemodial Int*. 2018;22:4–8. doi: 10.1111/hdi.12577
228. Wase A, Basit A, Nazir R, Jamal A, Shah S, Khan T, Mohiuddin I, White C, Saklayen M, McCullough PA. Impact of chronic kidney disease upon survival among implantable cardioverter-defibrillator recipients. *J Interv Card Electrophysiol*. 2004;11:199–204. doi: 10.1023/B:JICE.0000048570.43706.34

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229. Pun PH, Al-Khatib SM, Han JY, Edwards R, Bardy GH, Bigger JT, Buxton AE, Moss AJ, Lee KL, Steinman R, Dorian P, Hallstrom A, Cappato R, Kadish AH, Kudenchuk PJ, Mark DB, Hess PL, Inoue LY, Sanders GD. Implantable cardioverter-defibrillators for primary prevention of sudden cardiac death in CKD: a meta-analysis of patient-level data from 3 randomized trials. *Am J Kidney Dis*. 2014;64:32–39. doi: 10.1053/j.ajkd.2013.12.009
230. Nakhoul GN, Schold JD, Arrigain S, Harb SC, Jolly S, Wilkoff BL, Nally JV Jr, Navaneethan SD. Implantable cardioverter-defibrillators in patients with CKD: a propensity-matched mortality analysis. *Clin J Am Soc Nephrol*. 2015;10:1119–1127. doi: 10.2215/CJN.11121114
231. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjær H, Brandes A, Thøgersen AM, Gustafsson F, Egstrup K, Videbæk R, Hassager C, Svendsen JH, Høfsten DE, Torp-Pedersen C, Pehrson S; DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med*. 2016;375:1221–1230. doi: 10.1056/NEJMoa1608029
232. Chen TH, Wo HT, Chang PC, Wang CC, Wen MS, Chou CC. A meta-analysis of mortality in end-stage renal disease patients receiving implantable cardioverter defibrillators (ICDs). *PLoS One*. 2014;9:e99418. doi: 10.1371/journal.pone.0099418
233. Dhamija RK, Tan H, Philbin E, Mathew RO, Sidhu MS, Wang J, Saour B, Haqqie SS, Beathard G, Yevzlin AS, Salman L, Boden WE, Siskin G, Asif A. Subcutaneous implantable cardioverter defibrillator for dialysis patients: a strategy to reduce central vein stenoses and infections. *Am J Kidney Dis*. 2015;66:154–158. doi: 10.1053/j.ajkd.2015.01.028
234. Koman E, Gupta A, Subzposh F, Saltzman H, Kutalek SP. Outcomes of subcutaneous implantable cardioverter-defibrillator implantation in patients on hemodialysis. *J Interv Card Electrophysiol*. 2016;45:219–223. doi: 10.1007/s10840-015-0093-2
235. El-Chami MF, Levy M, Kelli HM, Casey M, Hoskins MH, Goyal A, Langberg JJ, Patel A, Delurgio D, Lloyd MS, Leon AR, Merchant FM. Outcome of subcutaneous implantable cardioverter defibrillator implantation in patients with end-stage renal disease on dialysis. *J Cardiovasc Electrophysiol*. 2015;26:900–904. doi: 10.1111/jce.12705
236. Boersma L, Barr C, Knops R, Theuns D, Eckardt L, Neuzil P, Scholten M, Hood M, Kuschyk J, Jones P, Duffy E, Husby M, Stein K, Lambiase PD; EFFORTLESS Investigator Group. Implant and midterm outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry: the EFFORTLESS Study. *J Am Coll Cardiol*. 2017;70:830–841. doi: 10.1016/j.jacc.2017.06.040
237. McAlister FA, Ezekowitz J, Hooton N, Vandermeer B, Spooner C, Dryden DM, Page RL, Hlatky MA, Rowe BH. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. *JAMA*. 2007;297:2502–2514. doi: 10.1001/jama.297.22.2502
238. Boerrigter G, Costello-Boerrigter LC, Abraham WT, Sutton MG, Heublein DM, Kruger KM, Hill MR, McCullough PA, Burnett JC Jr. Cardiac resynchronization therapy improves renal function in human heart failure with reduced glomerular filtration rate. *J Card Fail*. 2008;14:539–546. doi: 10.1016/j.cardfail.2008.03.009
239. Boerrigter G, Costello-Boerrigter LC, Abraham WT, St John Sutton MG, Heublein DM, Kruger KM, Hill MR, McCullough PA, Burnett JC Jr. Response to cardiac resynchronization therapy improves renal function: importance of forward and backward failure. *J Card Fail*. 2009;15:79–80. doi: 10.1016/j.cardfail.2008.11.001
240. Singal G, Upadhyay GA, Borgquist R, Friedman DJ, Chatterjee NA, Kandala J, Park MY, Orencole M, Dec GW, Picard MH, Singh JP, Mela T. Renal response in patients with chronic kidney disease predicts outcome following cardiac resynchronization therapy. *Pacing Clin Electrophysiol*. 2015;38:1192–1200. doi: 10.1111/pace.12685
241. Eisen A, Suleiman M, Strasberg B, Sela R, Rosenheck S, Freedberg NA, Geist M, Ben-Zvi S, Goldenberg I, Glikson M, Haim M; Israeli Working Group of Pacing and Electrophysiology of the Israel Heart Society. Renal dysfunction and clinical outcomes of patients undergoing ICD and CRTD implantation: data from the Israeli ICD registry. *J Cardiovasc Electrophysiol*. 2014;25:990–997. doi: 10.1111/jce.12442
242. Jeevanantham V, Turagam M, Shanberg D, Reddy M, Atoui M, Daubert JP, Dawn B, Lakkireddy D. Cardiac resynchronization therapy prevents progression of renal failure in heart failure patients. *Indian Pacing Electrophysiol J*. 2016;16:115–119. doi: 10.1016/j.ipej.2016.11.006
243. Kpaeyeh JA Jr, Divoky L, Hyer JM, Daly DD Jr, Maran A, Waring A, Gold MR. Impact of renal function on survival after cardiac resynchronization therapy. *Am J Cardiol*. 2017;120:262–266. doi: 10.1016/j.amjcard.2017.04.017
244. Bazoukis G, Letsas KP, Korantzopoulos P, Thomopoulos C, Vlachos K, Georgopoulos S, Karamichalakis N, Saplaouras A, Efremidis M, Sideris A. Impact of baseline renal function on all-cause mortality in patients who underwent cardiac resynchronization therapy: a systematic review and meta-analysis. *J Arrhythm*. 2017;33:417–423. doi: 10.1016/j.joa.2017.04.005
245. Stretch R, Sauer CM, Yuh DD, Bonde P. National trends in the utilization of short-term mechanical circulatory support: incidence, outcomes, and cost analysis. *J Am Coll Cardiol*. 2014;64:1407–1415. doi: 10.1016/j.jacc.2014.07.958
246. Patel AM, Adeseun GA, Ahmed I, Mitter N, Rame JE, Rudnick MR. Renal failure in patients with left ventricular assist devices. *Clin J Am Soc Nephrol*. 2013;8:484–496. doi: 10.2215/CJN.06210612
247. Mao H, Giuliani A, Blanca-Martos L, Kim JC, Nayak A, Virzi G, Brocca A, Scalzotto E, Neri M, Katz N, Ronco C. Effect of percutaneous ventricular assist devices on renal function. *Blood Purif*. 2013;35:119–126. doi: 10.1159/000346096
248. Mao H, Katz N, Kim JC, Day S, Ronco C. Implantable left ventricular assist devices and the kidney. *Blood Purif*. 2014;37:57–66. doi: 10.1159/000357970
249. Flaherty MP, Pant S, Patel SV, Kilgore T, Dassanayaka S, Loughran JH, Rawasia W, Dawn B, Cheng A, Bartoli CR. Hemodynamic support with a microaxial percutaneous left ventricular assist device (Impella) protects against acute kidney injury in patients undergoing high-risk percutaneous coronary intervention. *Circ Res*. 2017;120:692–700. doi: 10.1161/CIRCRESAHA.116.309738
250. Nemoto M. Experimental evaluation of the influence of complete artificial circulation on renal circulation and tissue metabolism -comparative study of pulsatile vs nonpulsatile circulation. *Ann Thorac Cardiovasc Surg*. 2003;9:355–364.
251. Kihara S, Litwak KN, Nichols L, Litwak P, Kameneva MV, Wu Z, Kormos RL, Griffith BP. Smooth muscle cell hypertrophy of renal cortex arteries with chronic continuous flow left ventricular assist. *Ann Thorac Surg*. 2003;75:178–183.
252. Welp H, Rukosujew A, Tjan TD, Hoffmeier A, Kösek V, Scheld HH, Drees G. Effect of pulsatile and non-pulsatile left ventricular assist devices on the renin-angiotensin system in patients with end-stage heart failure. *Thorac Cardiovasc Surg*. 2010;58(suppl 2):S185–S188. doi: 10.1055/s-0029-1240709
253. Axelrod DA, Schnitzler MA, Xiao H, Irish W, Tuttle-Newhall E, Chang SH, Kasiske BL, Alhamad T, Lentine KL. An economic assessment of contemporary kidney transplant practice. *Am J Transplant*. 2018;18:1168–1176. doi: 10.1111/ajt.14702
254. Schnitzler MA, Skeans MA, Axelrod DA, Lentine KL, Randall HB, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2016 annual data report: economics. *Am J Transplant*. 2018;18(suppl 1):464–503. doi: 10.1111/ajt.14702
255. Harnett JD, Foley RN, Kent GM, Barre PE, Murray D, Parfrey PS. Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. *Kidney Int*. 1995;47:884–890.
256. Stack AG, Bloembergen WE. A cross-sectional study of the prevalence and clinical correlates of congestive heart failure among incident US dialysis patients. *Am J Kidney Dis*. 2001;38:992–1000. doi: 10.1053/ajkd.2001.28588
257. US Renal Data System. *2017 USRDS Annual Data Report*: *Epidemiology of Kidney Disease in the United States*. Bethesda, MD: National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2017.
258. Trespalacios FC, Taylor AJ, Agodoa LY, Bakris GL, Abbott KC. Heart failure as a cause for hospitalization in chronic dialysis patients. *Am J Kidney Dis*. 2003;41:1267–1277.
259. de Mattos AM, Siedlecki A, Gaston RS, Perry GJ, Julian BA, Kew CE 2nd, Deierhoi MH, Young C, Curtis JJ, Iskandrian AE. Systolic dysfunction portends increased mortality among those waiting for renal transplant. *J Am Soc Nephrol*. 2008;19:1191–1196. doi: 10.1681/ASN.2007040503
260. Mathur AK, Chang YH, Steidley DE, Heilman R, Khurmi N, Wasif N, Etzioni D, Moss AA. Patterns of care and outcomes in cardiovascular disease after kidney transplantation in the United States. *Transplant Direct*. 2017;3:e126. doi: 10.1097/TXD.0000000000000640
261. Burt RK, Gupta-Burt S, Suki WN, Barcenas CG, Ferguson JJ, Van Buren CT. Reversal of left ventricular dysfunction after renal transplantation. *Ann Intern Med*. 1989;111:635–640.
262. Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray DC, Barre PE. Outcome and risk factors for left ventricular disorders in chronic uraemia. *Nephrol Dial Transplant*. 1996;11:1277–1285.
263. Melchor JL, Espinoza R, Gracida C. Kidney transplantation in patients with ventricular ejection fraction less than 50 percent: features and post-transplant outcome. *Transplant Proc*. 2002;34:2539–2540.

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264. Wali RK, Wang GS, Gottlieb SS, Bellumkonda L, Hansalia R, Ramos E, Drachenberg C, Papadimitriou J, Brisco MA, Blahut S, Fink JC, Fisher ML, Bartlett ST, Weir MR. Effect of kidney transplantation on left ventricular systolic dysfunction and congestive heart failure in patients with end-stage renal disease. *J Am Coll Cardiol*. 2005;45:1051–1060. doi: 10.1016/j.jacc.2004.11.061
265. Josephson CB, Delgado D, Schiff J, Ross H. The effectiveness of renal transplantation as a treatment for recurrent uremic cardiomyopathy. *Can J Cardiol*. 2008;24:315–317.
266. Lentine KL, Schnitzler MA, Abbott KC, Li L, Burroughs TE, Irish W, Brennan DC. De novo congestive heart failure after kidney transplantation: a common condition with poor prognostic implications. *Am J Kidney Dis*. 2005;46:720–733. doi: 10.1053/j.ajkd.2005.06.019
267. Rigatto C, Parfrey P, Foley R, Negrijn C, Tribula C, Jeffery J. Congestive heart failure in renal transplant recipients: risk factors, outcomes, and relationship with ischemic heart disease. *J Am Soc Nephrol*. 2002;13:1084–1090.
268. Siedlecki A, Foushee M, Curtis JJ, Gaston RS, Perry G, Iskandrian AE, de Mattos AM. The impact of left ventricular systolic dysfunction on survival after renal transplantation. *Transplantation*. 2007;84:1610–1617. doi: 10.1097/01.tp.0000295748.42884.97
269. Gonzalez Monte E, Mora MT, Polanco N, Morales E, Gutierrez E, Molina M, Sevillano A, Hernandez E, Praga M, Andres A. Impact of left ventricular dysfunction on renal transplant survival: study of paired kidneys from the same donor. *Transplant Proc*. 2015;47:70–72.
270. Paoletti E, Bellino D, Marsano L, Cassottana P, Rolla D, Ratto E. Effects of ACE inhibitors on long-term outcome of renal transplant recipients: a randomized controlled trial. *Transplantation*. 2013;95:889–895. doi: 10.1097/TP.0b013e3182827a43
271. Knoll GA, Fergusson D, Chassé M, Hebert P, Wells G, Tibbles LA, Treleaven D, Holland D, White C, Muirhead N, Cantarovich M, Paquet M, Kiberd B, Gourishankar S, Shapiro J, Prasad R, Cole E, Pilmore H, Cronin V, Hogan D, Ramsay T, Gill J. Ramipril versus placebo in kidney transplant patients with proteinuria: a multicentre, double-blind, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2016;4:318–326. doi: 10.1016/S2213-8587(15)00368-X
272. Issa N, Krowka MJ, Griffin MD, Hickson LJ, Stegall MD, Cosio FG. Pulmonary hypertension is associated with reduced patient survival after kidney transplantation. *Transplantation*. 2008;86:1384–1388. doi: 10.1097/TP.0b013e318188d640
273. Zlotnick DM, Axelrod DA, Chobanian MC, Friedman S, Brown J, Catherwood E, Costa SP. Non-invasive detection of pulmonary hypertension prior to renal transplantation is a predictor of increased risk for early graft dysfunction. *Nephrol Dial Transplant*. 2010;25:3090–3096. Abstract. doi: 10.1093/ndt/gfq141.
274. Lai Y-L, Wasse H, Kim WC Association of pulmonary hypertension at kidney transplant evaluation and subsequent outcome following kidney transplantation. *Am J Transplant*. 2015;15(suppl 3). Abstract. https://atcmeetingabstracts.com/abstract/association-of-pulmonary-hypertension-at-kidney-transplant-evaluation-and-subsequent-outcomes-following-transplantation/. Accessed April 10, 2018.
275. Grupper A, Grupper A, Daly RC, Pereira NL, Hathcock MA, Kremers WK, Cosio FG, Edwards BS, Kushwaha SS. Renal allograft outcome after simultaneous heart and kidney transplantation. *Am J Cardiol*. 2017;120:494–499. doi: 10.1016/j.amjcard.2017.05.006
276. Lentine KL, Villines TC, Axelrod D, Kaviratne S, Weir MR, Costa SP. Evaluation and management of pulmonary hypertension in kidney transplant candidates and recipients: concepts and controversies. *Transplantation*. 2017;101:166–181. doi: 10.1097/TP.0000000000001043
277. Bansal N, Hailpern SM, Katz R, Hall YN, Tamura MK, Kreuter W, O'Hare AM. Outcomes associated with left ventricular assist devices among recipients with and without end-stage renal disease. *JAMA Int Med*. 2018;178:204–209. doi: 10.1001/jamainternmed.2017.4831
278. Bekelman DB, Rumsfeld JS, Havranek EP, Yamashita TE, Hutt E, Gottlieb SH, Dy SM, Kutner JS. Symptom burden, depression, and spiritual well-being: a comparison of heart failure and advanced cancer patients. *J Gen Intern Med*. 2009;24:592–598. doi: 10.1007/s11606-009-0931-y
279. Leung L. From ladder to platform: a new concept for pain management. *J Prim Health Care*. 2012;4:254–258.
280. Davison SN, Koncicki H, Brennan F. Pain in chronic kidney disease: a scoping review. *Semin Dial*. 2014;27:188–204. doi: 10.1111/sdi.12196
281. Fukuta H, Goto T, Wakami K, Ohte N. Effects of drug and exercise intervention on functional capacity and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Eur J Prev Cardiol*. 2016;23:78–85. doi: 10.1177/2047487314564729
282. Fröhlich H, Katus HA, Täger T, Lossnitzer N, Grossekettler L, Kihm L, Zeier M, Remppis A, Frankenstein L, Schwenger V. Peritoneal ultrafiltration in end-stage chronic heart failure. *Clin Kidney J*. 2015;8:219–225. doi: 10.1093/ckj/sfv007
283. Hedayati SS, Jiang W, O'Connor CM, Kuchibhatla M, Krishnan KR, Cuffe MS, Blazing MA, Szczech LA. The association between depression and chronic kidney disease and mortality among patients hospitalized with congestive heart failure. *Am J Kidney Dis*. 2004;44:207–215.
284. Hedayati SS, Gregg LP, Carmody T, Jain N, Toups M, Rush AJ, Toto RD, Trivedi MH. Effect of sertraline on depressive symptoms in patients with chronic kidney disease without dialysis dependence: the CAST randomized clinical trial. *JAMA*. 2017;318:1876–1890. doi: 10.1001/jama.2017.17131
285. O'Connor CM, Jiang W, Kuchibhatla M, Silva SG, Cuffe MS, Callwood DD, Zakhary B, Stough WG, Arias RM, Rivelli SK, Krishnan R; SADHART-CHF Investigators. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. *J Am Coll Cardiol*. 2010;56:692–699. doi: 10.1016/j.jacc.2010.03.068
286. Chan KY, Cheng HW, Yap DY, Yip T, Li CW, Sham MK, Wong YC, Lau WK. Reduction of acute hospital admissions and improvement in outpatient attendance by intensified renal palliative care clinic follow-up: the Hong Kong experience. *J Pain Symptom Manage*. 2015;49:144–149. doi: 10.1016/j.jpainsymman.2014.04.010
287. Keuffel E, McCullough PA, Todoran TM, Brilakis ES, Palli SR, Ryan MP, Gunnarsson C. The effect of major adverse renal cardiovascular event (MARCE) incidence, procedure volume, and unit cost on the hospital savings resulting from contrast media use in inpatient angioplasty. *J Med Econ*. 2018;21:356–364.
288. Billings FT 4th, Shaw AD. Clinical trial endpoints in acute kidney injury. *Nephron Clin Pract*. 2014;127:89–93. doi: 10.1080/13696998.2017.1415912
289. Ronco C, Ronco F, McCullough PA. A call to action to develop integrated curricula in cardiorenal medicine. *Blood Purif*. 2017;44:251–259. doi: 10.1159/000480318
290. Tong A, Craig JC, Nagler EV, Van Biesen W; SONG Executive Committee and the European Renal Best Practice Advisory Board; SONG Executive Committee and the European Renal Best Practice Advisory Board. Composing a new song for trials: the Standardized Outcomes in Nephrology (SONG) initiative. *Nephrol Dial Transplant*. 2017;32:1963–1966. doi: 10.1093/ndt/gfx288

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